Medical Policy

BlueCross BlueShield of Kansas
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Title: Human Growth Hormone

Pre-Determination of Services IS REQUIRED by the Member's Contract

Prior Authorization Form:
BCBSKS will review Prior Authorization requests
http://www.bcbsks.com/CustomerService/Forms/pdf/15-811_Growth_Hormone_PA.pdf

Link to Drug List (Formulary):
http://www.bcbsks.com/drugs/

Professional	**Institutional**
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Populations	Interventions	Comparators	Outcomes
Individuals: • With proven growth hormone deficiency	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With short stature due to Prader Willi syndrome	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With short stature due to chronic renal insufficiency	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With short stature due to Turner syndrome	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With short stature due to Noonan syndrome	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With short stature due to SHOX (short stature homeobox-containing gene) deficiency	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With severe burns	Interventions of interest are: • Human growth hormone to treat or to prevent growth delay	Comparators of interest are: • Standard wound care	Relevant outcomes include: • Symptoms • Hospitalizations • Treatment-related morbidity
Individuals: • With AIDS wasting	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Treatment with a different medication	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With short bowel syndrome on specialized nutritional support	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care of short bowel syndrome	Relevant outcomes include: • Functional outcomes • Health status measures • Treatment-related morbidity
Individuals: • Who are small for gestational age in childhood	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With altered body habitus related to antiretroviral therapy for HIV infection	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With idiopathic short stature	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With "genetic potential" (ie, lower than expected height percentiles based on parents' height)	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With precocious puberty	Interventions of interest are: • Human growth hormone plus gonadotropin-releasing hormone	Comparators of interest are: • Gonadotropin-releasing hormone only	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • Who are older adults with age-related growth hormone deficiency	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With cystic fibrosis	Interventions of interest are: • Human growth hormone	Comparators of interest are: • Standard care without human growth hormone treatment	Relevant outcomes include: • Functional outcomes • Quality of life • Treatment-related morbidity

DESCRIPTION

Recombinant human growth hormone (GH) is approved by the U.S. Food and Drug Administration for various indications and is also proposed for various off-label indications, such as cystic fibrosis and treatment of older adults without documented growth hormone deficiency (GHD).

OBJECTIVE

The objective of this policy is to evaluate the net health outcome when human growth hormone is used to treat various Food and Drug Administration-approved and off-label indications compared with the net health outcome achieved by standard therapy for these conditions.

BACKGROUND

Growth Hormone

Human growth hormone (GH), also known as somatotropin, is synthesized in somatotropic cells of the anterior lobe of the pituitary gland. Growth hormone deficiency (GHD) can occur for various conditions, such as:

- Pituitary tumor
- Pituitary dysfunction due to prior surgery or radiation treatment
- Extrapituitary tumor
- Sarcoidosis and/or other infiltrating disorders
- Idiopathic

GHD in children is manifested primarily by short stature. In adults, as well as in some children, other abnormalities associated with GHD are often evident. They include changes in body composition, higher levels of low-density lipoprotein cholesterol, lower bone density, and a decreased self-reported quality of life compared with healthy peers. Some evidence suggests that there may be increases in cardiovascular disease and overall mortality, but it is less clear whether GHD is causative for these outcomes.

Major points of controversy are what defines "inadequate secretion of normal endogenous growth hormone," and what constitutes "growth failure." Before the availability of biosynthetic GH, GH was rationed to children with classic GHD, as defined by a subnormal response (<10 ng/mL, approximately, depending on GH assay) to GH provocation tests. However, the ready supply of GH has created interest in expanding its use to short-stature children without classic GHD, often referred to as partial GHD, neurosecretory GH dysfunction, constitutional delay in growth and development, or idiopathic short stature. "Classic" GHD is suggested when the abnormal growth velocity (typically <10th percentile) or height is more than 2 SDs below the current population mean, in conjunction with a chronologic age that is greater than the height age and bone age. Practically, interest in broadening the use of GH to non-GHD children has resulted in GH evaluation in many children who are simply below the 3rd percentile in height, with or without an abnormal growth velocity.

Selection Criteria

These broadened patient selection criteria have remained controversial due to uncertainties in almost every step in the diagnosis and treatment process—selection of patients to be tested, limitations in the laboratory testing for GH, establishment of diagnostic cutoffs for normal versus abnormal GH levels, availability of the laboratory tests to predict response to GH therapy, changes in growth velocity due to GH therapy, whether resulting final height is significantly improved, and whether this improvement is clinically or emotionally significant for the patient. In addition, there are many ethical considerations regarding GH therapy, most prominently appropriate informed consent when the therapy is primarily requested by parents due to their particular psychosocial concerns about height.

In 2001, somatropin (Genotropin) received an FDA-labeled indication for treatment of pediatric patients born small for gestational age who failed to show catch-up growth by age 2 years. Most children born small for gestational age normalize their stature during infancy, but about 15% maintain an exceptionally short stature at least throughout childhood. Epidemiologic surveys have suggested that the average adult height of men and women who did not exhibit catch-up growth as children is 5 feet, 6 inches, in men and 5 feet, 1 inch, in women. GH has been investigated in these children, based in part on the hypothesis that a GH resistance is a possible etiology of the growth retardation. In 2003, FDA approved a rhGH product for use in non-GH-deficient short stature, defined by the manufacturer as a height SDS of -2.25 below the mean. This indication for GH is the first indication based on short stature alone, without an underlying etiology.

Outcome Measures in GH Research

The most common outcome measure reported in GH research is change in height. For some situations, such as in patients with documented GHD or genetic disorder and short stature, improvements in height alone may be a sufficient outcome measure. However, in most situations, a change in height is not in itself sufficient to demonstrate that health outcomes are improved. There is insufficient evidence to establish that short stature is associated with substantial impairments in psychological functioning or quality of life, or

that increases in height improve these parameters. Similarly, improvements in other measures of body composition (eg, muscle mass, muscle strength) are not in themselves sufficient to establish that health outcomes are improved. Therefore, for most conditions in this literature review, changes in other outcomes measures (eg, functional status, quality of life, disease-specific clinical outcomes) are necessary to demonstrate an improvement in health outcomes.

REGULATORY STATUS

Several formulations of human GH have received FDA approval for various indications (see Table 1).

There are phase 2 and phase 3 trials including children and adults that are currently ongoing, evaluating new GH formulations that are administered weekly rather than daily.[1-3] The new long-acting formulations have not received FDA approval at this time.

Table 1. FDA-Approved Indications by Product

Indications	Genotropin (Pfizer)	Humatrope (Lilly)	Norditropin (Novo-Nordisk)	Nutropin (Genentech)	Saizen (Serono)	Serostim (Serono)	Zomacton[a] (Ferring)	Zorbtive (Serono)	Omnitrope (Sandoz)
Growth failure, pediatric patients with inadequate endogenous GH	Yes	Yes	Yes	Yes	Yes		Yes		Yes
Replacement therapy in adults with GHD	Yes	Yes	Yes	Yes	Yes				Yes
Growth failure due to Prader-Willi syndrome	Yes								Yes
Growth failure associated with chronic renal insufficiency				Yes					
Short stature due to Turner syndrome (45,XO)	Yes	Yes	Yes	Yes			Yes		Yes
Short stature in pediatrics patients with Noonan syndrome			Yes						
Short stature in pediatrics patients with *SHOX* deficiency		Yes					Yes		
HIV wasting or cachexia						Yes			
Treatment of short bowel syndrome								Yes	
Children born small for gestational age, who fail to show catch-up growth by age 2 y	Yes	Yes	Yes				Yes		Yes
Short stature (height × SDS ≤ -2.25) in non-GHD pediatric patients	Yes	Yes		Yes					Yes
Idiopathic short stature							Yes		

FDA: Food and Drug Administration; GH: growth hormone; GHD: growth hormone deficiency; SDS: standard deviation score; *SHOX*; short stature homeobox-containing gene.
[a] In 2015, FDA approved a name change for Tev-Tropin; Tev-Tropin in now known as Zomacton.

The intent of the Growth Hormone Prior Authorization (PA) Criteria is to appropriately select patients for therapy according to Food and Drug Administration (FDA) approved product labeling and /or clinical guidelines and/or clinical studies. When criteria for use are met, the preferred agent may be approved for use; use of the nonpreferred growth hormone products will be evaluated if the prescriber indicates a history of documented intolerance of, FDA labeled contraindication to, or hypersensitivity to the preferred growth hormone.

TARGET DRUGS

Preferred Growth Hormone	Nonpreferred Growth Hormone
▪ Omnitrope®	▪ Genotropin® ▪ Humatrope® ▪ Norditropin® NordiFlex, Norditropin Flexpro ▪ Nutropin AQ® ▪ Nutropin AQ Nuspin® ▪ Saizen®, Saizen Click.Easy ▪ Serostim® ▪ Zomacton ▪ Zorbtive®

POLICY

A. Pediatric Growth Hormone Therapy

Growth hormone therapy is contractually excluded for those under age 18, except for the following specific conditions:

1. Growth Hormone Deficiency or Insufficiency as defined by:

   a. Insulin tolerance test with documented hypoglycemia (blood sugars less than 40 mg/dL) and peak GH value of <10 ng/mL, **OR**

      At least two provocative stimulation tests using arginine, clonidine, glucagon, growth hormone releasing hormone (GHRH), or levodopa with peak GH values <10 ng/mL on all tests.

   AND

   b. Growth failure as defined by the following age groups:
      - 0-6 months: <34 cm/year
      - 6-12 months: <15 cm/year
      - 1-3 years: <12 cm/year
      - Over three years to puberty (see definition of puberty below): <5 cm/year
      - Puberty (defined as bone age of 10½ -12 years for girls and bone age of 12½ -14½ years for boys): <6 cm/year

Note: Growth rates should be tracked over at least one year. Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year.

2. Panhypopituitarism subject to meeting all of the following criteria:

   a. Deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone)

   b. Low IFG-1 concentration

   Note: Growth hormone stimulation testing is not required in these cases. Growth hormone therapy may be approved for life.

3. Turner, Prader-Willi, and Noonan Syndromes with Growth Failure subject to meeting all of the following criteria:
   a. Height less than the 2.5 percentile for age and sex

   b. Growth failure as defined by the following age groups:
      - 0-6 months: <34 cm/year
      - 6-12 months: <15 cm/year
      - 1 - 3 years: <12 cm/year
      - Over three years to puberty (see below definition of puberty): <5 cm/year
      - Puberty (defined as bone age of 10½ -12 years for girls and bone age of 12½ -14½ years for boys): <6 cm/year

   Note: Growth rates should be tracked over at least one year (except age groups < 1 year).
   Growth hormone stimulation testing is not required in these cases.

4. Chronic Renal Insufficiency or End Stage Renal Disease as defined by:

   a. Chronic renal insufficiency defined as GFR less than 60 mL/min/1.73m^2 prior to successful transplant

   b. End stage renal disease defined as serum creatinine greater than 1.5 mg/dL or GFR less than 75 mL/min/1.73m^2 prior to successful transplant

   c. With open epiphyses

   d. Height less than the 2.5 percentile for age and sex

   e. Growth failure as defined by the following age groups:

- 0-6 months: <34 cm/year
- 6-12 months: <15 cm/year
- 1 – 3 years: <12 cm/year
- Over three years to puberty (see below definition of puberty): <5 cm/year
- Puberty (defined as bone age of 10½ -12 years for girls and bone age of 12½ -14½ years for boys): <6 cm/year

f. Complicating factors have been treated including malnutrition and acidosis

Note: Growth rates should be tracked over at least one year (except age groups < 1 year).
Growth Hormone stimulation testing is not required.
Growth Hormone is discontinued at the time of transplantation or other conditions below for termination of GH therapy.

5. Neonate (≤4 months of age) with hypoglycemia in the absence of metabolic disorder AND growth hormone level is <20 ng/mL.

6. AIDS wasting.

7. Prevention of growth delay in children with severe burns (see Policy Guidelines).

8. Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines).

Termination of Growth Hormone Therapy

Growth hormone therapy is **not medically necessary** when any one of the following criteria is met:

1. Epiphyseal fusion has occurred.
2. Mid-parental height is achieved. Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (6.4 cm) (male) or minus 2.5 inches (6.4 cm) (female).
3. Failure to respond to growth hormone therapy with a growth rate of less than 2.5 cm/year.

Documentation

Documentation needed for predetermination is:

- Growth charts with at least 3 measurements over at least one year
- Growth hormone stimulation testing results
- Other supporting documentation

Length of Approval: Growth hormone therapy approved for life (eg, panhypopituitarism, or when adult GH therapy requirements are met) will need continued review for benefits.

B. Adult Growth Hormone Therapy

1. Growth hormone therapy is excluded for those over the age of 18 with the following exceptions:

    a. Hypothalamic or pituitary disease or injury and laboratory proven growth hormone deficiency by GH stimulation testing.

    b. Childhood onset of growth hormone deficiency and deficiency is demonstrated by GH stimulation retesting during adulthood

    c. Panhypopituitarism with deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) and low values for IGF-1

2. Growth hormone stimulation for GH deficiency must be documented by the following criteria:

    a. Insulin tolerance test with documented hypoglycemia (blood sugars less than 40 mg/dL) and peak growth hormone values < 5ng/mL, **OR**

    b. Arginine-GHRH stimulation test (peak growth hormone values <4.1ng/mL), **OR**

    c. Arginine L-Dopa stimulation test (peak growth hormone values <1.5ng/mL), **OR**

    d. Glucagon stimulation test (peak growth hormone values <3ng/mL), **OR**

    e. A below normal level of IFG-1 when associated with panhypopituitarism with documented multiple hormone deficiencies (3 or more deficiencies: TSH, ACTH, FSH/LH, antidiuretic hormone) as a result of pituitary or hypothalamic disease secondary to tumor, surgery, inflammation, radiation therapy, severe head trauma or structural abnormality (septo-optic dysplasia, ectopic neurohypophysis). Growth hormone stimulation testing is not necessary in these cases.

3. Continuation of approval for growth hormone therapy requires some indication of a clinical response to the growth hormone during the first 12 months of therapy: weight loss, improvement on lipid profile, increased bone mass, increased muscle strength or increase of IGF-1 into the normal range. Children

on GH therapy who continue growth GH therapy into adulthood or adults with hypopituitarism of recent onset will not exhibit the manifestations of adult GH deficiency and will not show the improvements listed above.

4. AIDS wasting.

5. Promotion of wound healing in patients with severe burns (see Policy Guidelines).

6. Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines).

A Nonpreferred Growth Hormone will be approved when BOTH of the following are met:
1. The patient's medication history indicates use of the *preferred* growth hormone (GH) agent and
2. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the *preferred* GH agent.

Length of Approval: 12 months
Growth hormone therapy approved for life will need continued review for benefits.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Policy Guidelines
1. Only about 25% of those children with documented GH deficiency will be found to have GH deficiency as adults. Therefore, once adult height has been achieved, subjects should be retested for GH deficiency to determine if continuing replacement therapy is necessary.
2. The FDA cautions that the safety and effectiveness of GH therapy in adults aged 65 and older has not been evaluated in clinical studies. Therefore, it is noted that elderly patients may be more sensitive to the action of GH therapy and may be more prone to develop adverse reactions.
3. Growth hormone is contraindicated in patients with Prader-Willi syndrome, who are severely obese or who have severe respiratory impairment. Sleep studies are recommended prior to initiation of growth hormone therapy for obese pediatric patients with Prader-Willi syndrome.
4. Insulin tolerance testing is contraindicated in patients with cardiovascular disease, cerebrovascular disease, seizure disorders or patients older than 65 years.
5. AIDS wasting is defined as a weight loss of more than 10% of baseline that cannot be explained by a concurrent illness other than HIV infection. Patients treated with growth hormone must simultaneously be treated with antiviral agents. Therapy is continued until this definition is no longer met.

6. Growth hormone for burn patients should be limited to those patients with third-degree burns.
7. Growth hormone for patients with short bowel syndrome should be limited to patients receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome. Specialized nutritional support may consist of a high-carbohydrate, low-fat diet adjusted for individual patient requirements. Optimal management may include dietary adjustments, enteral feedings, parenteral nutrition, fluid, and micronutrient supplements.
8. Member Contract Language:
   Growth Hormone therapy is covered only under one of the following circumstances:
   If under age 18 and diagnosed with:
   a. Both laboratory proven growth hormone deficiency or insufficiency and significant growth retardation; or
   b. Substantiated Turner's syndrome, Prader-Willi syndrome, or Noonan's syndrome with significant growth retardation; or
   c. Chronic renal insufficiency and end stage renal disease with significant growth retardation prior to successful transplantation; or
   d. Panhypopituitarism; or
   e. Neonatal hypoglycemia related to growth hormone deficiency.

   If age 18 and over with:
   a. Evidence of pituitary or hypothalamic disease or injury and laboratory proven growth hormone deficiency; or
   b. A history of prior growth hormone therapy for growth hormone deficiency or insufficiency in childhood and laboratory confirmation of continued growth hormone deficiency.

   Children, Adolescents and Adults:
   a. AIDS wasting syndrome
   b. Short bowel syndrome
   c. Severe burn patients

RATIONALE

The policy was updated with a literature review using MEDLINE; most recently through August 23, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Safety of Growth Hormone Treatment

Adverse events can occur with growth hormone (GH) treatment. In children, increased rates of skeletal problems (eg, worsening of scoliosis) can occur in association with a rapid growth spurt. In adults, arthralgias, edema, and carpal tunnel syndrome are common. Less common adverse events include pancreatitis and gynecomastia.[4,5] There is also concern that GH treatment may increase the rate of malignancy, particularly de novo leukemia, in patients without risk factors. However, to date, there is insufficient evidence of a causative relation between GH treatment and malignancy rates.

Swerdlow et al (2017) published results from the Safety and Appropriateness of Growth Hormone Treatments in Europe study, which compared the risk of cancer mortality and cancer incidence among patients receiving GH therapy with national population rates.[6] For the cancer mortality analysis, the cohort consisted of 23,984 patients from 8 European countries. For the cancer incidence analysis, only those patients from countries with highly complete cancer registries (Belgium, Netherlands, Sweden, Switzerland, United Kingdom) were included (n=10,406). Over 50% received GH treatment due to "isolated growth failure," defined as growth hormone deficiency (GHD), idiopathic short stature, and prenatal growth failure. Other common diagnoses leading to GH treatment included: Turner syndrome, pituitary hormone deficiency, and central nervous system tumor. For the cancer mortality cohort, mean follow-up was 17 years, mean age at follow-up was 27 years, and there were 251 cancer deaths. For the cancer incidence cohort, mean follow-up was 15 years, mean age at last follow-up was 26 years, and there were 137 incident cancers. For patients whose initial diagnosis was "isolated growth failure," overall cancer risk was not elevated. For patients whose initial diagnosis was not cancer, neither cancer mortality nor cancer incidence was related to age of treatment initiation and duration of treatment.

Several publications on the safety of GH therapy have used French registry data and vital statistics. Analysis of long-term mortality after GH treatment was conducted by Carel et al (2012).[7] A total of 6928 children were included in the study. Indications for GH therapy included idiopathic isolated GHD (n=5162), neurosecretory dysfunction (n=534), idiopathic short stature (n=871), and born small for gestational age (n=335). The mean dose of GH used was 25 µg/kg/d, and the mean treatment duration was 3.9 years. Patients were followed for a mean of 17.3 years. As of September 2009, follow-up data on vital status were available for 6558 (94.7%) of participants. Ninety-three (1.42%) of the 6558 individuals had died. The mortality rate was significantly higher in patients treated with GH than would be expected on the basis of year, sex, or age (standardized mortality ratio, 1.33; 95% confidence interval [CI], 1.08 to 1.64). Examination of the causes of death found a significant increase in mortality due to circulatory system diseases. In addition, there was a significant increase in the number of deaths due to

bone tumors (3 observed deaths vs 0.6 expected deaths) but no other types of cancers or overall cancer deaths. There was also a significant increase in the number of deaths due to cerebral or subarachnoid hemorrhage (4 observed deaths vs 0.6 expected).

Poidvin et al (2014) reported on the same data, focusing on risk of stroke in adulthood among childhood users of GH therapy.[8] This analysis included 6874 children with idiopathic isolated GHD or short stature; mean length of follow-up was 17.4 years. There were 11 (0.16%) validated cases of stroke and the mean age at the time of stroke was 24 years. Risk of stroke was significantly higher in adults who had used GH than in general population controls. Stroke risk was also compared with general population controls. Standard incidence ratios were 2.2 (95% CI, 1.3 to 3.6) compared with registry data from Dijon and 5.3 (95% CI, 3.0 to 8.5) using Oxford registry data. The increased risk was largely for hemorrhagic stroke (8/11 cases), and this elevated risk persisted when the 3 patients who had been small for gestational age were excluded from the analysis. In all of the analyses from this research team, there were a small number of events (ie, deaths or stroke), and thus conclusions from these data are not definitive on the long-term safety of GH therapy.

According to drug prescribing information, GH therapy use has been associated with sudden death in children with Prader-Willi syndrome.[9,10] These deaths occurred among children who were severely obese or had severe respiratory impairment; these markers are now considered contraindications to GH treatment in patients with Prader-Willi syndrome.

Growth Hormone Deficiency

Clinical Context and Test Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with proven GHD.

The question addressed in this evidence review is: Does use of human GH improve the net health outcomes in individuals with proven GH?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with proven GHD.

Interventions

The therapy being considered is human GH.

Comparators

The following practice is currently being used to treat GHD: standard care without human GH treatment.

Outcomes

The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing

Follow-up at 1 year is of interest to monitor outcomes.

Setting
Patients with GHD are actively managed by endocrinologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

GHD in Children
In children with GHD, treatment has been found to increase growth velocity and final height. Root et al (1998) followed approximately 20,000 children for 9 years as part of the National Cooperative Growth Study.[11] Growth velocity improved compared with pretreatment values, and this improvement was maintained for at least 4 years. For children treated for at least 7 years, improvements in the mean height standard deviation score (SDS) ranged from 1.3 to 2.5, depending on the specific underlying condition. If treatment is started at an early age, most children can achieve a final height close to that expected from parental height. In a study of 1258 patients in the Pfizer International Growth Database, Reiter et al (2006) found the standard deviation (SD) for differences between the final height achieved and the midrange of predicted height from parental values ranged between -0.6 and +0.2, depending on the specific underlying condition.[12]

GHD in Adults
In adults with GHD, evidence from RCTs has shown that treatment leads to increases in lean body mass and decreases in body fat.[13]

Systematic Reviews
Meta-analyses of RCTs have shown evidence for increases in muscle strength and exercise capacity, although these findings were not robust across all studies.[14,15] There is also evidence from meta-analyses that GH therapy is associated with increased bone mineral density (BMD) in adults with GHD.[16,17] For example, a meta-analysis by Barake et al (2014) identified 9 placebo-controlled randomized trial with at least 1-year follow-up on the effect of daily GH therapy on BMD.[17] Analysis of RCT data found a statistically significant increase in BMD of the lumbar spine and femoral neck in patients with GHD who received GH therapy for more than 2 months. Change in BMD ranged from 1% to 5% at the spine and 0.6% to 4% at the femoral neck. A limitation of the Barake analysis is that data were not available on fracture rates, a clinically important outcome. The evidence on other outcomes (eg, quality of life, lipid profiles, cardiovascular disease, total mortality) has been inconsistent and insufficient to determine whether these outcomes improved with treatment.[18-21]

Observational Studies
Ishii et al (2017) published an industry-funded, multicenter, observational study of GH therapy for adults with GHD.[22] One hundred sixty-one patients were eligible for quality of life analysis using the Adult Hypopituitarism Questionnaire (AHQ). For male and female patients combined, AHQ scores were improved from baseline in both psycho-social and physical domains. Women had significantly lower AHQ scores than men throughout, however, the net changes in AHQ

scores did not differ significantly between men and women (psycho-social domain: 4.90 vs 4.36; p=0.833; physical domain: 5.04 vs 2.29; p=0.213; respectively), despite an increase in GH dose such that insulin-like growth factor-1 levels for women reached that of men. The study was limited due to loss to follow-up, data collection being on patient recall, the observational design, and lack of a control group.

Section Summary: Growth Hormone Deficiency
Large cohort studies, RCTs, and meta-analyses have found that, for children with documented GHD and clinical manifestations such as short stature, GH replacement has improved growth velocity and final height achieved. In addition, studies have shown that GH therapy can ameliorate the secondary manifestations of GHD and may increase lean muscle mass and BMD seen primarily in older children and adults.

Short Stature Due to Prader-Willi Syndrome
Prader-Willi syndrome is a rare neurodevelopmental disorder characterized by muscular hypotonia, hypogonadism, short stature, obesity, psychomotor delay, neurobehavioral abnormalities, and cognitive impairment. Most children with Prader-Willi syndrome have hypothalamic dysfunction and are GH-deficient. The value of testing for GHD before treatment in these patients is questionable. None of the clinical studies selected patients for treatment based on presence or absence of GHD, nor were results reported separately for those with or without GHD. Information from the product label indicates that the height SDS for Prader-Willi syndrome children in the clinical studies was -1.6 or less (height was in the 10th percentile or lower).

Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with short stature due to Prader-Willi syndrome.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in children with short stature due to Prader-Willi syndrome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is children with short stature due to Prader-Willi syndrome.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat Prader-Willi syndrome: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Follow-up at 8 years is of interest to monitor outcomes.

Setting
Patients with short stature due to Prader-Willi syndrome are actively managed by endocrinologists, occupational and behavioral specialists, and geneticists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Randomized Controlled Trials
Several RCTs in children have shown improvements in health outcomes with GH treatment. For example, Kuppens et al (2016) published results from a 2-year crossover, blinded, placebo-controlled randomized trial designed to investigate the effects of GH on body composition in young adults with Prader-Willi syndrome who were treated with GH during childhood and had attained adult height.[23] Patients (N=27) were stratified by sex and body mass index and randomized to GH injections once daily or placebo injections. After 1 year, the patients received the alternate treatment. Every 3 months, fat mass and lean body mass were measured by dual-energy x-ray absorptiometry. GH treatment resulted in lower mean fat mass (-17.3%) and higher lean body mass (+3.5%) compared with placebo.

Lo et al (2015) conducted a 2-year RCT of GH therapy vs no treatment followed by a cohort study of the children on GH therapy for an additional 6 years.[24] The trial included 42 prepubertal children (age range, 3.5-14 years); children were not selected based on GHD status. The primary outcome was the impact of GH treatment on behavior, measured by 2 validated parent questionnaires: the Developmental Behavior Checklist (DBC) and the Children's Social Behavior Questionnaire (CSBQ). At the end of the 2-year RCT, there were no significant differences in DBC and CSBQ scores between the GH-treated and no-treatment groups. Findings were similar at the end of the 8-year follow-up period.

Moreover, an RCT by Reus et al (2013) found that the addition of GH therapy to physical training resulted in greater improvements in motor development than physical training alone.[25] This 2-year, single-blind trial included 22 children newly diagnosed with Prader-Willi syndrome (mean age, 12.9 months). GHD status was not considered in the study eligibility criteria. Outcomes were evaluated every 3 months, and multiple regression analysis was conducted to evaluate whether GH had an impact on motor development over time. Among the results was a finding that GH had statistically significant interaction effects for a model predicting motor development age using the Alberta Infant Motor Scale.

An earlier RCT by Festen et al (2008) included 42 infants and 49 prepubertal children (age range, 3-14 years).[26] GHD status was not part of the study eligibility criteria. The study found that GH treatment significantly improved height, body mass index, head circumference, and body composition. In 2012, the same investigators published cognitive outcomes in children participating in this trial.[27] During the 2-year randomized study, mean total IQ score and subtests did not change significantly from baseline in GH-treated children. In untreated children, there was no significant change in total IQ score, but scores on 2 of 3 subtests significantly declined from baseline.

Case Reports
There have been numerous case reports of sudden unexpected death in Prader-Willi syndrome patients undergoing GH therapy.[28-30] Causes of death included respiratory insufficiency and sleep apnea, suggesting that GH therapy may exacerbate respiratory impairment in patients with Prader-Willi syndrome. The product labels for GH treatments, therefore, warn that children with

Prader-Willi syndrome be evaluated for signs of upper airway obstruction and sleep apnea prior to initiation of treatment and that treatment should be discontinued if these signs occur.[9,10]

Section Summary: Short Stature due to Prader-Willi Syndrome
Several RCTs have found improvements in height, body mass index, head circumference, and motor development in children with Prader-Willi syndrome treated with GH. GH treatment was not found to significantly change problem behavior or total IQ. In a blinded crossover RCT, patients with Prader-Willi syndrome, who were treated with GH as children and had attained adult height experienced lower fat mass and higher lean body mass when treated with GH compared with placebo. Studies have found increased risk of adverse events in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment, and thus these are contraindications.

Short Stature Due to Chronic Renal Insufficiency
Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with short stature due to chronic renal insufficiency.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with short stature due to chronic renal insufficiency?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with short stature due to chronic renal insufficiency.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short stature due to chronic renal insufficiency: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Follow-up at 9 years is of interest to monitor outcomes.

Setting
Patients with short stature due to chronic renal insufficiency are actively managed by endocrinologists, occupational and behavioral therapists, and nephrologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews

Wu et al (2013) published a systematic review of RCTs evaluating the impact of GH therapy on height outcomes following renal transplant in children ages 0 to 18 years.[31] Five trials (total N=401 participants) met reviewers' inclusion criteria (RCTs including renal allograft recipients between 0 and 18 years old). Trials were published between 1996 and 2002. A meta-analysis found significantly improved height velocity at the end of a trial in children taking GH compared with a no-treatment control group. At the beginning of the year, both groups had a negative height SDS, with no statistically significant differences between groups. After 1 year, the pooled mean difference (MD) in height SDS was 0.68 (95% CI, 0.25 to 1.11; p=0.002) in favor of the GH group. There were no statistically significant differences between groups in the rate of rejection episodes or in renal function.

Previously, Hodson et al (2012) published a Cochrane review of RCTs evaluating GH treatment in children with chronic kidney disease.[32] To be included in the review, trials needed to include children 18 years old or younger who were diagnosed with chronic kidney disease and were predialysis, on dialysis, or posttransplant. In addition, trials had to compare GH treatment with placebo, no treatment, or a different GH regimen, and needed to include height outcomes. Seven RCTs with 809 children met reviewers' criteria. Study entry criteria varied (eg, ranging from <3rd percentile for chronologic age to <50th percentile for chronologic age). Overall, treatment with GH (28 IU/m^2/wk) compared with placebo or no specific therapy resulted in a statistically significant increase in height SDS at 1 year (8 studies; MD=0.82; 95% CI, 0.56 to 1.07). Moreover, a pooled analysis of 7 studies found a significant increase in height velocity at 1 year in the group receiving GH treatment compared with control (MD=3.88 cm/y; 95% CI, 3.32 to 4.44 cm/y).

Randomized Controlled Trials

An example of an individual RCT is Hokken-Koelega et al (1991), conducted in the Netherlands.[33] This double-blind, placebo-controlled crossover trial included 20 prepubertal children with severe growth retardation and chronic renal failure. Entry criteria included height velocity less than the 25% percentile for chronologic age. Patients received 6 months of subcutaneous injection of GH (4 IU/m^2/d) before or after 6 months of placebo injection. There was a 2.9 cm greater increase in height velocity per 6 months with GH than with placebo. Long-term follow-up data on children in this and other Dutch RCTs (maximum of 8 years of treatment) were published in 2000.[34] GH treatment resulted in significant improvement in the height SDS compared with baseline scores (p<0.001). Moreover, the mean height SDS reached the lower end (-2 SDS) of the normal growth chart after 3 years of treatment. Puberty began at a median age within the normal range for girls and boys, and GH therapy did not significantly affect parathyroid hormone concentrations, and there were no radiologic signs of renal osteodystrophy.

Nonrandomized Studies

Primary outcomes in most studies of GH for the treatment of children with chronic kidney disease are height or height velocity. A case-control study by Bizzarri et al (2018) compared the final height of children treated (n=68) and not treated (n=92) with GH who had chronic kidney disease.[35] Mean follow-up was 9 years. Among cases, the mean duration of GH therapy was 4 years. Height SDS significantly improved from baseline to final height in GH-treated children, while there was a slight but nonsignificant decrease in height SDS among non-GH-treated children. However, final height SDS did not differ significantly between treated and nontreated children (p=0.3). The reason for no difference in final height might have been that the nontreated children had a significantly higher height SDS at baseline compared with the

treatment group. This difference might be why GH treatment was not initiated in the control group.

Section Summary: Short Stature due to Chronic Renal Insufficiency
Numerous RCTs and systematic reviews of RCTs have found significantly increased height and height velocity in children with short stature associated with chronic renal insufficiency who were treated with GH therapy compared with another intervention. There were no significant increases in adverse events related to renal function.

Short Stature Due to Turner Syndrome
Short stature is a characteristic of Turner syndrome, although the syndrome is not associated with GHD. Poor growth is evident in utero, and further deceleration occurs during childhood and at adolescence. The mean adult height for those with Turner syndrome is 58 inches (4 feet, 10 inches). FDA approvals for GH were based on the results of RCTs that included final adult height as the outcome. In one study, a group of patients with Turner syndrome given somatropin (Humatrope) at a dosage of 0.3 mg/kg/wk for a median of 4.7 years achieved a final height of 146.0 cm (57.5 in) compared with an untreated control group who achieved a final height of 142.1 cm (56 in).[10]

Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with short stature due to Turner syndrome.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with short stature due to Turner syndrome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with short stature due to Turner syndrome.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short stature due to Turner syndrome: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Treatment of an average 6 years is of interest to monitor outcomes.

Setting
Patients with short stature due to Turner syndrome are actively managed by endocrinologists, occupational and behavioral specialists, and geneticists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
Li et al (2018) conducted a meta-analysis to determine the effect of recombinant human GH treatment on height outcomes in patients with Turner syndrome.[36] Eleven RCTs (total N=1122 patients), published between 1986 and 2011, were identified for the analysis. Compared with controls, there was a significant increase in final height (mean difference [MD], 7.2 cm; 95% CI, 5.27 to 9.18 cm; p<0.001), height SD (standardized mean difference [SMD], 1.22 cm; 95% CI, 0.88 to 1.56 cm; p<0.001), and height velocity (MD=2.68 cm/y; 95% CI, 2.34 to 3.02 cm/y; p<0.001) for patients receiving GH. After 1 year, bone age increased slightly for the GH group (SMD=0.32/y; 95% CI, 0.1 to 0.54/y; p=0.004). The meta-analysis was limited by the small number of available studies and the lack of sufficient data on final height.

A Cochrane review by Baxter et al (2007) identified 4 RCTs (total N=365 patients) evaluating GH for treating Turner syndrome.[37] Studies included children who had not yet achieved final height, had treated children for at least 6 months, and compared GH with placebo or no treatment. Only 1 trial reported final height, so outcomes could not be pooled. A pooled analysis of 2 trials reported that short-term growth velocity was greater in treated than in untreated children (MD=3 cm/y; 95% CI, 2 to 4 cm/y).

Nonrandomized Studies
In addition to short stature, individuals with Turner syndrome also exhibit craniofacial characteristics such as shorter and flattened cranial bases and inclined maxilla and mandible. A cross-sectional study by Juloski et al (2016) compared the craniofacial morphology of 13 patients who had Turner syndrome treated using GH with 13 patients who had Turner syndrome not treated using GH.[38] Mean age of participants was 17 years. Individuals in the treatment group had received GH for a mean of 5.8 years. Comparisons of lateral cephalometric radiographs showed that GH therapy significantly increased linear measurements, mainly influencing posterior and anterior face height, mandibular height and length, and maxillary length. Angular measurements and facial height ratio did not differ significantly between groups.

Section Summary: Short Stature Due to Turner Syndrome
Several RCTs have been published and/or are reported in FDA documents. Studies have found that GH therapy increases height outcomes (eg, final height, height velocity) in children with short stature due to Turner syndrome compared with placebo or no treatment. GH therapy has also been found to have a positive effect on craniofacial development.

Short Stature Due to Noonan Syndrome
Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with short stature due to Noonan syndrome. Noonan syndrome is associated with slow growth, starting in early childhood.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with short stature due to Noonan syndrome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with short stature due to Noonan syndrome.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short stature due to Noonan syndrome: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Follow-up to 3 years is of interest to monitor outcomes.

Setting
Patients with short stature due to Noonan syndrome are actively managed by endocrinologists, occupational and behavioral specialists, and geneticists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
Giacomozzi et al (2015) published a systematic review of literature on the effect of GH therapy on adult height.[39] Included in the review were studies treating individuals with a diagnosis of Noonan syndrome with no other causes of short stature and a normal karyotype in females. In addition, studies had to follow patients for at least 3 years. Twenty-three studies were identified in a literature search conducted through April 2014, and 6 studies (total N=177 patients) met the inclusion criteria; none were RCTs, one was controlled, and the rest prospective or retrospective cohort studies or case reports.

In the single controlled study (MacFarlane et al [2001][40]), over the 3-year follow-up, the GH-treated group gained a mean of 3.3 cm more than the untreated group. Among the uncontrolled studies, 2 reported adult height. Mean height SDS was -2.8 (SD=0.6) and mean adult height SDS was -1.4 (SD=0.9). Two uncontrolled studies reported near-adult height, which was -2.1 (SD=0.9). In addition, 2 studies reported a change in height SDS corresponding to 8.6 cm (SD=5.9). Mean height gain in SDS ranged from 0.6 to 1.4 cm by national standards, and between 0.6 and 2.0 cm by Noonan standards. The data were limited by the paucity of controlled studies and lack of RCTs.

Section Summary: Short Stature due to Noonan Syndrome
Evidence consists of a systematic review including a controlled trial and 5 uncontrolled studies. The data were limited due to lack of comparative studies; however, the systematic review found that GH therapy is associated with an increase in height in patients with short stature due to Noonan syndrome.

Short Stature Due to Short Stature Homeobox-Containing Gene Deficiency

Clinical Context and Test Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with short stature due to short stature homeobox-containing gene (*SHOX*) deficiency.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with short stature due to *SHOX* deficiency?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with short stature due to *SHOX* deficiency.

Interventions

The therapy being considered is human GH.

Comparators

The following practice is currently being used to treat short stature due to *SHOX* deficiency: standard care without human GH treatment.

Outcomes

The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing

Follow-up to 5 years is of interest to monitor outcomes.

Setting

Patients with short stature due to *SHOX* deficiency are actively managed by endocrinologists, occupational and behavioral specialists, and geneticists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined in indication 1.

Randomized Controlled Trials

A health technology assessment by Takeda et al (2010) assessed GH treatment of growth disorders in children identified an RCT evaluating GH therapy for children with short stature due to *SHOX* deficiency.[41] This industry-sponsored, open-label multicenter trial was published by Blum et al (2007).[42] It included 52 prepubertal children age at least 3 years who had *SHOX* deficiency. Height requirements were less than the 3rd percentile of the local reference range or less than 10th percentile with height velocity less than the 25th percentile. Participants were randomized to 2 years of GH treatment (n=27) or usual care (n=25). The primary outcome was first-year height velocity. Fifty-one of 52 patients completed the trial. The first-year height velocity was 8.7 cm/y in the GH therapy group and 5.2 cm/y in the usual care group ($p<0.001$). Height gain over the 2-year treatment period was 16.4 cm in the treatment group and 10.5 cm in the usual care group ($p<0.001$). No serious adverse events were reported for either group. At the end of the randomized phase, all patients were offered GH.

Nonrandomized Studies
Benabbad et al (2017) published long-term height results and safety data from patients in the Blum RCT (described above) and from a subset of patients with short stature due to *SHOX* deficiency from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS).[43] GeNeSIS was a prospective, multinational, open-label, pediatric surveillance program examining long-term safety and efficacy of GH. The subset of the GeNeSIS population with *SHOX* deficiency consisted of 521 patients. Forty-nine of the 52 patients in the RCT enrolled in the long-term study. Patients in both studies will be followed until they achieve near-adult (final) height. Final height was defined as attaining one of the following criteria: height velocity less than 2 cm/y, hand x-ray showing closed epiphyses, or bone age older than 14 years for boys or older than 16 years for girls. At the time of the analysis, 90 patients from GeNeSIS and 28 patients from the RCT reached near-adult height. For the GeNeSIS patients, mean age at GH treatment initiation was 11.0 years, mean age at near-adult height was 15.7 years, and GH treatment duration was 4.4 years. For the RCT patients, mean age at GH initiation was 9.2 years, mean age at near-adult height was 15.5 years, and GH duration was 6.0 years. The most common treatment-emergent adverse events reported in the GeNeSIS patients were: precocious puberty (2.6%) and arthralgia (2.4%). The most common treatment-emergent adverse events reported in the RCT patients were: headache (18.4%) and congenital bowing of long bones (18.4%).

Section Summary: Short Stature due to Short Stature Homeobox-Containing Gene Deficiency
An RCT found that children with short stature due to *SHOX* deficiency had significantly greater height velocity and significantly more height gain after 2 years when treated with GH vs no GH treatment. A long-term observational study reported that patients with *SHOX* deficiency were able to reach near-adult height after 4 to 6 years of GH treatment.

Severe Burns
Clinical Context and Test Purpose
The purpose of human GH to treat or to prevent growth delay is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with severe burns.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with severe burns?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with severe burns.

Interventions
The therapy being considered is human GH to treat or to prevent growth delay.

Comparators
The following practice is currently being used to treat or prevent growth delay due to severe burns: standard wound care. Typical treatment for severe burns includes skin transplantation and grafting.

Outcomes
The general outcomes of interest are symptoms, hospitalizations, and treatment-related morbidity.

Timing
Follow-up at 2 years is of interest to monitor outcomes.

Setting
Patients with severe burns are actively managed by burn center specialists and orthopedic surgeons in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Treatment of Severe Burns
Systematic Reviews
A Cochrane review by Breederveld et al (2012) included RCTs evaluating the impact of GH therapy on the healing rates of burn wounds.[44] Thirteen trials were identified that compared GH therapy with another intervention or to placebo. Six included only children, and seven involved only adults. Twelve studies were placebo-controlled. Findings of 2 studies reporting wound healing time in days were pooled. The mean healing time was significantly shorter in the GH-treated group than in the placebo group (MD = -9.07 days; 95% CI, -4.39 to -13.76). Reviewers also performed meta-analyses of studies that did not conduct survival analyses but did follow patients until their wounds healed. These analyses found significantly shorter healing time in patients who received GH therapy among adults (2 studies) and among children (2 studies). A pooled analysis of 5 studies did not find a statistically significant difference in mortality among patients receiving GH therapy and placebo (relative risk [RR], 0.53; 95% CI, 0.22 to 1.29). The mortality analysis likely was underpowered; the total number of deaths was 17. A pooled analysis of 3 studies involving adults found significantly shorter hospital lengths of stay in patients who received GH therapy compared with placebo (MD = -12.55 days; 95% CI, -17.09 to -8.00 days). In another pooled analysis, there was a significantly higher incidence of hyperglycemia in GH-treated patients than in controls (RR=2.65; 95% CI, 1.68 to 4.16).

Randomized Controlled Trials
An RCT by Knox et al (1995) measuring mortality included 54 adult burn patients who survived the first 7 postburn days.[45] Those patients showing difficulty with wound healing were treated with human GH and compared with those healing at the expected rate with standard therapy. Mortality of GH-treated patients was 11% compared with 37% for those not receiving GH (p=0.027). Infection rates were similar in both groups.

Singh et al (1998) studied 2 groups of patients (N=22) with comparable third-degree burns; those who received GH had improved wound healing and a lower mortality rate (8% vs. 44%).[46] A placebo-controlled trial by Losada et al (2002) found no benefit to GH with regard to length of hospitalization in 24 adults with severe burns.[47]

Prevention of Growth Delay in Children with Severe Burns
Children with severe burns show significant growth delays for up to 3 years after injury. GH treatment in 72 severely burned children for 1 year after discharge from intensive care resulted in significantly increased height in a placebo-controlled, randomized, double-blinded trial.[48] Aili Low et al (2001) also found that GH treatment in severely burned children during hospitalization resulted in significantly greater height velocity during the first 2 years after burn compared with a similar group of untreated children.[49]

Section Summary: Severe Burns
Numerous RCTs evaluating GH for treatment of severe burns have been identified. Pooled analyses found significantly shorter healing times and significantly shorter hospital stays with GH therapy vs placebo. Several RCTs have found significantly greater height gains in children with burns who received GH therapy vs placebo or no treatment.

AIDS Wasting
Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with AIDS wasting.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with AIDS wasting?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with AIDS wasting.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat AIDS wasting: treatment with different medications.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Follow-up at 12 weeks is of interest to monitor outcomes.

Setting
Patients with AIDS wasting are actively managed by HIV specialists and infectious disease specialists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
Moyle et al (2004) published a systematic review and meta-analysis of controlled and uncontrolled studies on selected treatments of HIV wasting.[50] To be included, studies had to assess more than 10 patients and have a treatment duration lasting at least 2 weeks. Pooled analysis of 3 studies using GH therapy showed significant increases in lean body mass compared with placebo (MD=3.1; 95% CI, 2.7 to 3.6). Pooled analysis of 6 studies reporting pre-post lean body mass measurements also showed significant increases following GH treatment (MD=2.7; 95% CI, 1.4 to 3.7). Two studies evaluating GH treatment found statistically significant improvements in some measurements of quality of life after 12 weeks.

Randomized Controlled Trials
A double-blind RCT by Evans et al (2005) included 700 patients with HIV-associated wasting.[51] Patients were randomized to daily GH, alternate days of GH, or placebo. Patients assigned to daily GH had significantly greater increases in maximum exercise capacity (the primary outcome) than patients assigned to placebo.

Section Summary: AIDS Wasting
A systematic review and meta-analysis of the literature found significant improvements in lean body mass with GH therapy vs placebo and improvements in quality of life. A subsequent RCT with a large sample size found a significantly greater increase in maximum exercise capacity with GH treatment than with placebo.

Short Bowel Syndrome with Specialized Nutritional Support
Short bowel syndrome is experienced by patients who have had 50% or more of the small intestine removed. This procedure results in malnourishment because the remaining small intestine is unable to absorb enough water, vitamins, and other nutrients from food. The FDA label for somatropin (Zorbtive) indicates that GH has been shown in human clinical trials to enhance the transmucosal transport of water, electrolytes, and nutrients. According to the product label, the FDA's approval for Zorbtive was based on the results of a randomized, controlled, phase 3 trial in which patients dependent on intravenous parenteral nutrition who received Zorbtive (either with or without glutamine) over a 4-week period had significantly greater reductions in the weekly total volume of intravenous parenteral nutrition required for nutritional support. However, the effects beyond 4 weeks were not evaluated nor were treatment locations (inpatient vs outpatient) identified.

Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with short bowel syndrome on specialized nutritional support.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with short bowel syndrome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with short bowel syndrome on specialized nutritional support.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat short bowel syndrome: standard of care.

Outcomes
The general outcomes of interest are functional outcomes, health status measures, and treatment-related morbidity.

Timing
Follow-up at 4 weeks is of interest to monitor outcomes.

Setting
Patients with short bowel syndrome on specialized nutritional support are actively managed by endocrinologists, and dieticians in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
A Cochrane review by Wales et al (2010) identified 5 RCTs evaluating GH therapy for treating short bowel syndrome.[52] Studies evaluated GH with or without glutamine treatment. The primary outcome was change in body weight. A pooled analysis of 3 small trials (n=30 patients) found a statistically significant difference in weight change when patients were treated with GH compared with placebo (MD=1.7 kg; 95% CI, 0.7 to 2.6 kg; $p<0.001$). Lean body mass, nitrogen absorption, and energy absorption also significantly increased in patients receiving GH therapy compared with controls.

Several published trials have also demonstrated improved intestinal absorption in short bowel syndrome patients receiving parenteral nutrition.[53,54] However, the Cochrane review and the studies noted that the effects of increased intestinal absorption were limited to the treatment period.[52,54,55] Specialized clinics may offer intestinal rehabilitation for patients with short bowel syndrome; GH may be a component of this therapy.

Section Summary: Short Bowel Syndrome with Specialized Nutritional Support
A pooled analysis of 3 small RCTs found a significantly greater weight gain with GH therapy compared with placebo; others studies have found improved intestinal absorption on patients with short bowel syndrome receiving parenteral nutrition.

Small for Gestational Age Children
Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are small for gestational age in childhood.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in children who are small for gestational age?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is children who are small for gestational age.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat children small for gestational age: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Treatment of an average 7.3 years is of interest to monitor outcomes.

Setting
Children who are small for gestational age are actively managed by endocrinologists and primary care physicians in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
A meta-analysis of RCTs evaluating GH treatment for children born small for gestational age was published by Maiorana and Cianfarani (2009).[56] Four trials (total N=391 children) met selection criteria (birth height or weight <2 SDS, initial height <2 SDS). The GH dose ranged from 33 to 67 µg/kg in the RCTs, and mean duration of treatment was 7.3 years. Mean adult height in the 4 studies was -1.5 SDS in the treated group and -2.4 SDS in the untreated group. Adult height in the treated group was significantly higher than that of controls (MD=0.9 SDS [5.7 cm]; p<0001). There was no difference in adult height between the 33 and 67 µg/kg/d doses. Reviewers noted that it is unclear whether the gain in adult height associated with GH treatment "is of sufficient clinical importance and value to warrant wide-spread treatment of short children born SGA [small for gestational age]…."

There are very few data on the psychosocial outcomes of short pediatric or adult stature related to intrauterine growth retardation and how these outcomes may be affected by GH therapy. As noted, data are inadequate to document that youths with short stature have either low self-esteem or a higher than average number of behavioral or emotional problems.

Section Summary: Small for Gestational Age Children
While a meta-analysis found that GH treatment resulted in significantly greater adult height in children born small for gestational age than a control treatment, the clinical implications of these findings has been called into question. Additionally, there are few data on psychological or functional outcomes associated with this additional gain in height.

Altered Body Habitus Related To Antiretroviral Therapy For Hiv Infection
Research has evaluated the use of GH for altered body habitus, which may be a complication of antiretroviral therapy for HIV infection. Body habitus changes, also referred to as fat redistribution syndrome or HIV-associated lipodystrophy syndrome, include thinning of the face, thinning of the extremities, truncal obesity, breast enlargement, or an increased dorsocervical fat pad ("buffalo hump").[57] However, there is relatively little published literature on the use of GH for this indication, mostly letters to editors and small case series.

Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with altered body habitus related to antiretroviral therapy for HIV infection.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with altered body habitus due to antiretroviral therapy for HIV infection?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with altered body habitus related to antiretroviral therapy for HIV infection.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat altered body habitus due to antiretroviral therapy for HIV infection: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Treatment of 40 weeks is of interest to monitor outcomes.

Setting
Patients with HIV-related altered body habitus are actively managed by HIV specialists and infectious disease specialists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Randomized Controlled Trials
Because high-dose GH has been associated with adverse events relating to inflammation, Lindboe et al (2016) conducted a randomized, double-blind, placebo-controlled trial to test the effect of low-dose GH in the treatment of HIV-infected patients on retroviral therapy.[58] Participants were randomized to GH 0.7 mg/day (n=24) or placebo (n=18) for 40 weeks. The primary outcome was change in inflammation measured by C-reactive protein and soluble urokinase plasminogen activator receptor (suPAR), both of which increase with inflammation. After 40 weeks, low-dose GH significantly lowered C-reactive protein. Low-dose GH lowered suPAR as well, but the difference was not statistically significant, even after controlling for age, weight, smoking status, and lipodystrophy.

Case Series
A large case series was reported by Wanke et al (1999) who treated 10 HIV-infected patients with fat redistribution syndrome with GH for 3 months.[59] The authors reported improved waist/hip ratio and mid-thigh circumference.

Section Summary: Altered Body Habitus Related to Antiretroviral Therapy for HIV Infection
An RCT comparing low-dose GH with placebo showed that the treatment could reduce inflammation experienced by HIV-infected patients who had altered body habitus related to

antiretroviral therapy. A case series has reported reductions in visceral abdominal fat. Additional studies reporting a wider range of outcomes are needed.

Children with Idiopathic Short Stature

Clinical Context and Test Purpose

The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with idiopathic short stature.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with idiopathic short stature?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is individuals with idiopathic short stature (without documented GHD or underlying pathology).

Interventions

The therapy being considered is human GH.

Comparators

The following practice is currently being used to treat idiopathic short stature: standard care without human GH treatment.

Outcomes

The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing

Follow-up at 2 years is of interest to monitor outcomes.

Setting

Patients with idiopathic short stature are actively managed by endocrinologists and geneticists in an outpatient clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined in indication 1. Impact on Adult Height

Systematic Reviews

Several meta-analyses have assessed the impact of GH on idiopathic short stature and adult height. More recently, Deodati and Cianfarani (2011) identified 3 RCTs and 7 non-RCTs.[60] Selection criteria for the systematic review included prepubertal children with initial short stature (>2 SD below the mean) and peak GH response greater than 10 µg/L. In addition, participants could not have had previous GH therapy or comorbid conditions that could impair growth. Adult height was defined as a growth rate of less than 1.5 cm/year or bone age of 15 years in females and 16 years in males. The primary efficacy outcome was the difference between groups in adult height, measured as SDS. The investigators considered an MD in height of more than 0.9 SDS (≈6 cm) to be a satisfactory response to GH therapy. Only 1 randomized trial was placebo-

controlled, and that trial had a high dropout rate (40% in the treated group, 65% in the placebo group).

In the 3 RCTs (n=115 patients), the mean adult height (primary efficacy outcome) was -1.52 SDS for treated children and -2.30 SDS for untreated children. The difference between groups significantly favored the treated group (MD=0.65 SDS [≈4 cm]; 95% CI, 0.40 to 0.91; p<0.001). The mean adult height in the 7 nonrandomized studies was -1.7 SDS for treated children and -2.1 SDS for untreated children. The MD between groups was 0.45 SDS (3 cm) (95% CI, 0.18 to 0.73) and was statistically significant favoring the treated group (p<0.001). Although GH treatment resulted in a statistically significant increase in adult height in the treated group, according to the a priori definition of a satisfactory response (difference, 0.9 SDS), the difference was not clinically significant. Moreover, there was a lack of high-quality, placebo-controlled randomized trials.

A Cochrane review by Bryant et al (2007) evaluated GH therapy for idiopathic short stature in children and adolescents.[61] Ten RCTs met eligibility criteria, which included studies conducted in children who had normal GH secretion, normal size for gestational age at birth, and no evidence of chronic organic disease. In addition, studies had to compare GH treatment with placebo or no treatment and provide GH treatment for at least 6 months. Three studies were placebo-controlled, and the other seven compared GH therapy with no treatment. Unlike the Deodati and Cianfarani review (previously described), studies were not required to report final adult height. Nine of 10 studies in the Cochrane review were short term and reported intermediate outcomes. A pooled analysis of 3 studies reporting growth velocity at 1 year found a statistically significant greater growth velocity in treated than in untreated children. The weighted mean difference was 2.84 (95% CI, 2.06 to 2.90). Five studies reported height SDSs, but there was heterogeneity among studies, and findings were not pooled. These data would suggest that GH has an effect on height in children with idiopathic short stature in the short term but that evidence on GH's effects on adult height is extremely limited.

Impact on Self-Esteem and Quality of Life

Advocates of GH therapy often cite the potential psychosocial impairments associated with short stature. Several RCTs have investigated this issue and did not find better self-esteem, psychological functioning, or quality of life in children treated with GH compared with controls. These studies are briefly described next.

Randomized Controlled Trials

Ross et al (2004) published findings on psychological adaptation in 68 children with idiopathic short stature without GHD.[62] Children (mean age, 12.4 years) were randomized to GH therapy (n=37) or placebo (n=31) 3 times per week until height velocity decreased to less than 1.5 cm/y. At baseline and then yearly, parents and children completed several psychological instruments including the Child Behavior Checklist (CBCL) and the Self-Perception Profile. No significant associations were found between attained height SDS or change in height SDS and annual changes in CBCL scores. There were no significant differences between groups on any CBCL summary scales in years 1 and 2, but, in year 4, there were significantly higher scores on the CBCL summary scales in the group receiving GH treatment. There were no significant differences between groups on the Self-Perception Profile at any follow-up point. This trial did not find a correlation between short stature and psychological adaptation or self-concept.

Theunissen et al (2002) in the Netherlands published a trial in which 40 prepubertal children with idiopathic short stature were randomized to GH treatment (n=20) or a control group (n=20).[63]

Parents and children were interviewed at baseline and at 1 and 2 years to obtain information on health-related quality of life and children's self-esteem. At the 2-year follow-up, satisfaction with current height was significantly associated with improvement in children's reported health-related quality of life, social functioning, and other psychosocial measures. However, satisfaction with height did not differ significantly between the treatment and control groups. The data from this trial did not support the hypothesis that GH treatment improves health-related quality of life in children with idiopathic short stature.

Downie et al (1996) examined the behavior of children without documented GHD who were treated with GH due to idiopathic short stature.[64] Across measures of behavior, including IQ, self-esteem, self-perception, or parental perceptions of competence, there were no significant differences between the control and the treatment groups, either at baseline or after 5 years of GH therapy. The authors concluded that while no psychosocial benefits of GH therapy have been demonstrated, likewise, no documented psychosocial ill effects of GH treatment have been demonstrated.

Section Summary: Children with Idiopathic Short Stature
Systematic reviews have found that GH treatment may increase height gain for children with idiopathic short stature, but the difference in height gain may not be clinically significant. The absolute difference in height in these studies ranged from 3 to 4 cm; further, children treated with GH remained below average in height, with heights between 1 and 2 SD below the mean at the end of treatment (note: these studies did not follow treated patients long enough to determine the ultimate impact of GH on final adult height).

RCTs have not found that short stature is associated with psychological problems, contrary to the expectations of some advocates. In addition, the available trials have not reported a correlation between increases in height and improvements in psychological functioning. Moreover, this group of children is otherwise healthy, and there are potential risks to GH therapy in childhood (see previous section Safety of Growth Hormone Treatment).

Children with "Genetic Potential"
Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with "genetic potential".

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with "genetic potential"?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with "genetic potential".

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat children with "genetic potential": standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Due to the lack of relevant data, it is not possible to determine an appropriate window for follow-up.

Setting
Patients with "genetic potential" are actively managed by endocrinologists and geneticists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Clinical Studies
No randomized or nonrandomized studies were identified that have evaluated the efficacy, safety, and/or psychosocial impacts of treating children with "genetic potential" (ie, children with lower than expected high percentiles based on their parents' height).

Section Summary: Children with "Genetic Potential"
There is insufficient evidence to draw conclusions about the use of human GH to treat "genetic potential."

Precocious Puberty
Precocious puberty is generally defined as the onset of secondary sexual characteristics before eight years of age in girls and 9 years in boys. Central precocious puberty is related to hypothalamic pituitary gonadal activation, leading to increase in sex steroid secretion, which accelerates growth and causes premature fusion of epiphyseal growth plates, thus impacting final height. Children with precocious puberty are often treated with gonadotropin-releasing hormone (GnRH) analogues to suppress the pituitary gonadal activity, to slow the advancement of bone age, and to improve adult height.

Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with precocious puberty.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in children with precocious puberty?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is children with precocious puberty.

Interventions
The therapy being considered is human GH plus GnRH

Comparators
The following practice is currently being used to treat precocious puberty: GnRH only.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Follow-up at 2 years is of interest to monitor outcomes.

Setting
Patients with precocious puberty are actively managed by endocrinologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
Liu et al (2016) published a meta-analysis comparing GnRH with the combination therapy of GH plus GnRH for the treatment of females who had idiopathic central precocious puberty.[65] The literature search, conducted through December 2014, identified 6 RCTs (n=162) and 6 clinical controlled trials (n=247) for inclusion. Risk of bias in the RCTs was assessed using the Cochrane Collaboration checklist. Five of the RCTs were determined to have moderate risk of bias and 1 trial had a high risk of bias. The controlled trials were assessed using the Methodological Index for Nonrandomized Studies (MINORS), based on 12 items, with an ideal global score of 24. Scores on MINORS for the 6 controlled trials ranged from 17 to 20, because none of the trials reported blinded outcome evaluation or prospective calculation of study size. Primary outcomes included final height, difference between final height and targeted height, and height gain. Among the 12 included studies, age of participants ranged from 4.6 to 12.2 years and treatment with the combination therapy ranged from 6 months to 3 years. One RCT and 4 controlled trials provided data for the meta-analyses. Results showed that patients receiving the combination therapy for at least 1 year experienced significantly greater final height, difference in final height and targeted height, and height gain compared with those receiving GnRH alone (MD=2.8 cm [95% CI, 1.8 to 3.9 cm]; MD=3.9 cm [95% CI, 3.1 to 4.7 cm]; MD=3.5 cm [95% CI, 1.0 to 6.0 cm], respectively). When treatment duration was less than 1 year, no significant differences in the height outcomes were found.

Randomized Controlled Trials
One RCT compared GnRH analogues alone with GnRH analogues plus GH therapy. This trial, by Tuvemo et al (1999), included 46 girls with precocious puberty.[66] Criteria for participation did not include predicted adult height or growth velocity. After 2 years of treatment, mean growth and predicted adult height were greater in those receiving combined treatment than in those receiving GnRH analogues alone. The absence of final height data limited interpretation of this trial.

Case Series
A case series by Pucarelli et al (2003) reported on 17 girls with precocious puberty and a growth velocity below the 25th percentile who were treated with a combination of GnRH and GH, and 18 girls who refused treatment with adjunctive GH.[67] Those in the combined group attained a significantly greater adult height (161.2 cm) than the "control" group (156.7 cm).

Section Summary: Precocious Puberty
Evidence for the incremental benefit of GH added to GnRH therapy in patients with precocious puberty consists of a systematic review, an RCT, and case series. One RCT and 4 controlled trials of moderate quality provided data for the meta-analyses. Small, but statistically significant differences were reported in final height (2.8 cm), in the difference between final height and targeted height (3.9 cm), and in height gain (3.5 cm) for patients who received the combination therapy for at least one year compared with patients receiving GnRH alone. Interpretation of results from the RCT and small comparative case series not included in the systematic review is limited because of methodologic issues. No studies have reported on the impact of short stature on functional or psychological outcomes.

Older Adults with Age-Related GHD
Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients who are older adults with age-related GHD.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in older adults with age-related GHD?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is older adults with age-related GHD.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat older adults with age-related GHD: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Due to the lack of relevant data, it is not possible to determine the window for follow-up.

Setting
Older adults with age-related GHD are actively managed by endocrinologists and primary care physicians in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
A TEC Assessment (2001) investigated the use of GH in older adults with age-related GHD and concluded that there was insufficient evidence of efficacy.[68] It is not possible to prove effectiveness of GH treatment or lack thereof unless otherwise similar groups of treated vs

nontreated patients are compared over a sufficient length of time to allow detection of any significantly and clinically different results.

Section Summary: Older Adults with Age-Related GHD
A TEC Assessment concluded that there is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled studies were identified.

Cystic Fibrosis
Clinical Context and Test Purpose
The purpose of human GH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with cystic fibrosis.

The question addressed in this evidence review is: Does use of human GH improve the net health outcome in individuals with cystic fibrosis?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with cystic fibrosis.

Interventions
The therapy being considered is human GH.

Comparators
The following practice is currently being used to treat cystic fibrosis: standard care without human GH treatment.

Outcomes
The general outcomes of interest are functional outcomes, quality of life, and treatment-related morbidity.

Timing
Treatment of 1 year is of interest to monitor outcomes.

Setting
Patients with cystic fibrosis are actively managed by endocrinologists, pulmonologists, and physical therapist in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined in indication 1.

Systematic Reviews
A Cochrane review by Thaker et al (2013) evaluated GH therapy for improving lung function, nutritional status, and quality of life in children and young adults with cystic fibrosis.[69] Reviewers identified 4 RCTs (total N=161 participants). All studies used daily subcutaneous injection of human GH as the intervention and included a no treatment or placebo control group. All trials measured pulmonary function and nutritional status. Due to differences in how outcomes were measured, study findings were not pooled. Across trials, GH improved intermediate outcomes such as height and weight; however, improvements in lung function were inconsistent. No significant changes in quality of life or clinical status were detected.

Previously, a systematic review by Phung et al (2010) identified 10 controlled trials evaluating GH for treating patients with cystic fibrosis.[70] One study was placebo-controlled, eight compared GH therapy with no treatment, and the remaining trial compared GH alone with glutamine or glutamine plus GH. Treatment durations ranged from 4 weeks to 1 year. There were insufficient data to determine the effect of GH on most health outcomes (eg, frequency of intravenous antibiotic treatment, quality of life, bone fracture). Data were pooled for a single outcome, frequency of hospitalizations. In trials lasting at least 1 year, there were significantly lower rates of hospitalizations per year in groups receiving GH therapy (pooled effect size, -1.62; 95% CI, -1.98 to -1.26).

Randomized Controlled Trials

An industry-sponsored, open-label RCT was published by Stalvey et al (2012).[71] It compared GH therapy with no treatment in prepubertal children with cystic fibrosis younger than 14 years old. Eligibility criteria included height less than the 10th percentile for age and sex; children with documented GHD were excluded. Participants were treated daily for 12 months and followed for another 6 months. The trial included 68 children; 62 (91%) were included in the efficacy analysis, and all but one were included in the safety analysis. The annualized height velocity at month 12 was 8.2 cm/y in the treatment group and 5.3 cm/y in the control group ($p<0.001$). The mean height SDS in the treatment group was -1.8 at baseline, -1.4 at 12 months, and -1.4 at 18 months vs -1.9 at all 3 time points in the control group. The change in mean height SDS from baseline to 12 months was significantly greater in the treatment than in the control group ($p<0.001$). Between months 12 and 18, the control group remained at the same height SDS, while the treatment group experienced a slight decline (0.1 SDS), but maintained a 0.5 SDS advantage over the control group.

In terms of pulmonary outcomes, the unadjusted rate of change from baseline to 12 months for most variables (7 of 8 pulmonary test results) did not differ between groups. However, the unadjusted change from 12 to 18 months (after treatment ended) was significantly greater in the control group than in the treatment group for 4 of 7 pulmonary test variables, including forced expiratory volume in 1 second (FEV_1) ($p<0.005$) and forced vital capacity ($p<0.01$). In the treatment group, mean FEV_1 was 1209 liters at baseline, 1434 liters at 12 months, and 1467 liters at 18 months compared with 1400 liters at baseline, 1542 liters at 12 months, and 1674 liters at 18 months in the control group. From baseline to 12 months, the between-group difference in change in the 6-minute walk distance did not differ significantly (26.3 meters; 95% CI, -44.8 to 97.4 meters). Ten children in the treatment group and nine in the control group were hospitalized for pulmonary exacerbations during the 12-month trial; the difference between groups was not statistically significant. In general, treatment with GH resulted in statistically significant improvements in height SDS but did not significantly improve clinical outcomes associated with cystic fibrosis.

Section Summary: Cystic Fibrosis

Several RCTs and systematic reviews have been identified. The RCTs were heterogenous and reported a variety of outcomes. None of the systematic reviews pooled results for outcomes (eg, frequency of intravenous antibiotic treatment, quality of life, bone fracture). The single pooled outcome (number of hospitalizations) was significantly lower in patients receiving GH therapy vs no treatment or placebo. Across the trials, GH improved intermediate outcomes such as height and weight; however, clinically meaningful outcomes relating to lung function did not consistently improve with GH.

SUMMARY OF EVIDENCE

For individuals who have proven GHD who receive human GH, the evidence includes RCTs, large observational studies, and meta-analyses. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Studies have found that, for patients with documented GHD and clinical manifestations such as short stature, GH replacement improves growth velocity and final height achieved. In addition, studies have shown that GH therapy can ameliorate the secondary manifestations of GHD such as increase in lean muscle mass and bone mineral density seen primarily in older children and adults. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to Prader-Willi syndrome who receive human GH, the evidence includes RCTs and a cohort study. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Several RCTs have found improvements in height, body mass index, head circumference, and motor development in children with Prader-Willi syndrome treated with GH. One RCT reported that GH treatment continued to benefit individuals with Prader-Willi syndrome who had attained adult height, by significantly lowering fat mass and increasing lean body mass. GH treatment was not found to significantly affect problem behavior or total IQ. Studies have found increased risk of adverse events in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment and thus GH is contraindicated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to chronic renal insufficiency who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Systematic reviews of RCTs have found significantly increased height and height velocity in children with short stature associated with chronic renal insufficiency who are treated with GH therapy compared with other interventions. There were no significant increases in adverse events related to renal function. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to Turner syndrome who receive human GH, the evidence includes RCTs and observational studies. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. RCTs and observational studies have found that GH therapy increases height outcomes (eg, final height, height velocity) and positively affects craniofacial development in children with short stature and craniofacial complex due to Turner syndrome compared with placebo or no treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to Noonan syndrome who receive human GH, the evidence includes a systematic review of controlled and uncontrolled studies. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. While the studies in the systematic review were generally of low quality and included only 1 trial comparing patients receiving GH with patients receiving no treatment, reviewers found that GH therapy was associated with an increase in height in patients with Noonan syndrome. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short stature due to *SHOX* deficiency who receive human GH, the evidence includes an RCT and a long-term observational study. Relevant outcomes are functional

outcomes, quality of life, and treatment-related morbidity. The RCT found that children with short stature due to *SHOX* deficiency had significantly greater height velocity and height gain after 2 years when treated with GH than with no GH. The long-term study reported that, after 4 to 6 years of GH treatment, patients with *SHOX* deficiency may attain near-adult height. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have severe burns who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are symptoms, hospitalizations, and treatment-related morbidity. Numerous RCTs evaluating GH for treatment of severe burns have been identified. Pooled analyses have found significantly shorter healing times and significantly shorter hospital stays with GH therapy than with placebo. Several RCTs have found significantly greater height gain in children with burns who received GH therapy vs placebo or no treatment. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have AIDS wasting who receive human GH, the evidence includes observational studies, RCTs, and a systematic review. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A systematic review with meta-analysis found significant improvements in lean body mass with GH therapy vs placebo; several studies found improvements in quality of life. An RCT with a large sample size reported a significantly greater increase in exercise capacity with GH than with placebo. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have short bowel syndrome on specialized nutritional support who receive human GH, the evidence includes RCTs and a meta-analysis. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A pooled analysis of 3 small trials found significantly greater weight gain with GH therapy than with placebo, and other studies found improved intestinal absorption in patients with short bowel syndrome receiving parenteral nutrition. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are small for gestational age in childhood who receive human GH, the evidence includes RCTs and a meta-analysis. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. The meta-analysis found that GH treatment in small for gestational age children resulted in significantly greater adult height compared with no treatment; however, the clinical significance of the height difference between the study groups is unclear. There are few data on the psychological or functional outcomes associated with this additional gain in height. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have altered body habitus related to antiretroviral therapy for HIV infection who receive human GH, the evidence includes an RCT and case series. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. The RCT measured the effect of low-dose GH on intermediate outcomes (inflammation markers). Case series data are insufficient for drawing conclusions about the impact of GH treatment on health outcomes in HIV-infected patients with altered body habitus due to antiretroviral therapy. Controlled studies reporting relevant outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have idiopathic short stature who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. Systematic reviews have found that GH treatment may increase height gain for children with idiopathic short stature, but the difference in height gain may not be clinically significant. The available studies did not follow treated patients long enough to determine the ultimate impact of GH on final adult height. RCTs have not found that short stature is associated with psychological problems, contrary to the expectations of some advocates. In addition, the available trials have not reported a correlation between increases in height and improvements in psychological functioning. Moreover, this group of children is otherwise healthy, and there are potential risks to GH therapy in childhood. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have "genetic potential" (ie, lower than expected height percentiles based on parents' height) who receive human GH, the evidence includes no clinical trials. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. No published literature was identified on GH therapy as a treatment of children with "genetic potential." The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have precocious puberty who receive human GH plus gonadotropin-releasing hormone, the evidence includes a systematic review, an RCT, and a comparative case series. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. While the systematic review included RCTs and controlled trials, only 1 RCT and 4 controlled trials provided data for the meta-analyses of final height, difference in final height and targeted height, and height gain. The meta-analyses reported statistically significant gains of several centimeters for patients who received the combination therapy for at least 1 year compared with patients receiving gonadotropin-releasing hormone alone. However, no studies have reported on the impact of short stature on functional or psychological outcomes in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are older adults with age-related GHD who receive human GH, the evidence includes a systematic review (TEC Assessment). Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. The TEC Assessment concluded there is a lack of evidence that GH therapy in older adults improves health outcomes. No subsequent controlled studies were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have cystic fibrosis who receive human GH, the evidence includes RCTs and systematic reviews. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. The RCTs were heterogenous and reported various outcomes. None of the systematic reviews pooled results for outcomes such as frequency of intravenous antibiotic treatment, quality of life, and bone fracture. The single pooled outcome (number of hospitalizations) was significantly lower in patients receiving GH therapy vs no treatment or placebo. Across trials, GH was found to improve intermediate outcomes such as height and weight; however, clinically meaningful outcomes relating to lung function were not consistently improved with GH. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Pediatric Endocrine Society

In 2015, the Pediatric Endocrine Society published an evidence-based report on risk of neoplasia in patients receiving GH therapy.[72] The report concluded that GH therapy can be administered without concerns about impact on neoplasia in children without known risk factors for malignancy. For children with medical conditions associated with an increased risk of future malignancies, patients should be evaluated on an individual basis and decisions made about the tradeoff between a possible benefit of GH therapy and possible risks of neoplasm.

As an addendum to the 2015 guidelines, Grimberg and Allen (2017), coauthors of the guidelines, published a historical review of the use of GH.[73] They asserted that although the guidelines did not find an association between GH and neoplasia, the use of GH should not necessarily be expanded. While the use of GH for patients with growth hormone deficiency (GHD) is recommended, evidence gaps persist in the use of GH for other indications such as idiopathic short stature and partial isolated GHD.

In 2016, the PES published guidelines for GH and insulin-like growth factor I-treatment for children and adolescents with GHD, idiopathic short stature, and primary insulin-like growth factor-I deficiency.[74] The guidelines used the GRADE approach (grading of recommendations, assessment, development, and evaluation). The following recommendations were made:

- "We recommend the use of GH to normalize adult height and avoid extreme shortness in children and adolescents with GHD. (strong recommendation, high quality evidence)
- "We suggest a shared decision-making approach to pursuing GH treatment for a child with idiopathic short stature. The decision can be made on a case by case basis after assessment of physical and psychological burdens, and discussion of risks and benefits. We recommend against the routine use of GH in every child with height SDS [standard deviation score] ≤ -2.25. (conditional recommendation, moderate quality evidence)

In 2017, PES published clinical practice guidelines for the management of Turner syndrome based on proceedings of the International Turner Syndrome Meeting.[75] PES recommended initiating GH treatment early, around 4 to 6 years of age, and preferably before 12 to 13 years if the child has evidence of growth failure (<50th percentile height velocity) or has strong likelihood of short stature (moderate quality of evidence).

Endocrine Society

An Endocrine Society clinical practice guideline on adult growth hormone deficiency, updated in 2011, includes the following statements[76]:

- The Task Force recommends that GH therapy of GH-deficient adults offers significant clinical benefits in body composition and exercise capacity.
- The Task Force suggests that GH therapy of GH-deficient adults offers significant clinical benefits in skeletal integrity.
- The Task Force recommends after documentation of persistent GHD that GH therapy be continued after completion of adult height to obtain full skeletal/muscle maturation during the transition period.

National Institute of Health and Clinical Excellence

In 2010, the National Institute of Health and Clinical Excellence (NICE) in the U.K. issued guidance on human growth hormone for growth failure in children.[77] NICE recommends GH as a possible treatment for children with growth failure who have any of the following conditions:

- Growth hormone deficiency

- Turner syndrome
- Prader-Willi syndrome
- Chronic renal insufficiency
- Small for gestational age and have growth failure at 4 years
- Short stature homeobox (SHOX) gene deficiency

American Association of Clinical Endocrinologists

In 2009, the American Association of Clinical Endocrinologists (AACE) issued updated guidelines on growth hormone use in growth hormone-deficient adults and transition patients.[78] Evidence-based recommendations include the following:

- Growth hormone deficiency (GHD) is a well-recognized clinical syndrome in adults that is associated with significant comorbidities if untreated
- Growth hormone (GH) should only be prescribed to patients with clinical features suggestive of adult growth hormone deficiency and biochemically proven evidence of adult growth hormone deficiency
- No data are available to suggest that GH has beneficial effects in treating aging and age-related conditions and the enhancement of sporting performance; therefore, the guideline developers do not recommend the prescription of GH to patients for any reason other than the well-defined approved uses of the drug.

Growth Hormone Research Society et al

In 2008, the Growth Hormone Research Society, Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop published a consensus statement on the diagnosis and treatment of children with idiopathic short stature.[79] Within the working group that developed the statement, the appropriate height below which GH treatment should be considered ranged from -2 to -3 SDS. The optimal age for treatment was thought to be between 5 years and early puberty. The group noted that psychological issues should be considered, eg, GH therapy should not be recommended for short children who are unconcerned about stature.

In 2013, a Growth Hormone Research Society (GHRS) workshop issued consensus guidelines on recombinant human growth hormone (rhGH) therapy in Prader-Willi syndrome (PWS).[80] The following were among the group's recommendations:

- "After genetic confirmation of the diagnosis of PWS, rhGH treatment should be considered and, if initiated, should be continued for as long as demonstrated benefits outweigh the risks."
- "GH stimulation testing should not be required as part of the therapeutic decision-making process in infants and children with PWS."
- "Exclusion criteria for starting rhGH in patients with PWS include severe obesity, uncontrolled diabetes, untreated severe obstructive sleep apnea, active cancer, and active psychosis."
- Scoliosis and cognitive impairment should not be considered exclusion criteria.

In 2016, results from the Growth Hormone Safety Workshop were published in the *European Journal of Endocrinology*.[81] The workshop was convened by GHRS and other medical societies. The purpose of the workshop was to reappraise the safety of rhGH. The position statement concluded:

- After following children and adults for tens of thousands of person-years, the safety profile of rGH remains good when rhGH is used for approved indications and at recommended doses. There is no evidence supporting an association between rhGH and

overall mortality, risk of new primary cancer, risk of recurrence of primary cancer, risk of stroke, or risk of cardiovascular disease.
- A carefully designed cohort study, providing continued long-term surveillance of patients treated with rhGH, would address the current limitations of safety data (eg, inconsistent definitions of outcomes, low incidence outcomes, and lack of dose-specific assessments).

American Academy of Pediatrics

In 2016, the American Academy of Pediatrics published guidelines on the evaluation and referral of children with signs of early puberty.[82] The use of gonadotropin-releasing hormone analogues were discussed as treatment options, but GH as a treatment option was not discussed.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03038594	Growth Hormone Therapy for Muscle Regeneration in Severely Burned Patients	62	Oct 2019
NCT03535415[a]	A Phase 3 Study to Evaluate the Efficacy and Safety of Recombinant Human Growth Hormone in Short Stature Children Due to Chronic Kidney Disease Before Transplantation	68	Dec 2021
NCT03245333[a]	Phase III Clinical Study of Recombinant Human Growth Hormone Injection (JINTOPIN AQ) for Short Children with Small for Gestational Age (SGA)	120	Dec 2017 (ongoing)
NCT02770157[a]	Phase III Clinical Trial for Assessment of Efficacy and Safety of DA-3002 (Recombinant Human Growth Hormone) in Short Children Born Small for Gestational Age	75	Sep 2019
NCT01196156[a]	An Observational Phase IV Study for Prospective Follow-Up to Adult Height of a Cohort of Subjects Born Small for Gestational Age and Treated with Growth Hormone	443	Feb 2020
NCT00537914[a]	Long-term Phase IV Multicenter Study on the Safety and Efficacy of Omnitrope® (rhGH) in Short Children Born Small for Gestational Age (SGA)	278	Mar 2021
NCT01604395[a]	An Open, Multi-Center, Prospective and Retrospective Observational Study to Evaluate the Long-term Safety and Effectiveness of Growth Hormone (Eutropin Inj./Eutropin plus Inj.) Treatment with GHD, TS, CRF, SGA, and ISS in Children	2000	Jan 2022
Unpublished			
NCT01246219[a]	The Influence of Growth Hormone (GH) Therapy on Short Stature Related Distress a Prospective Randomized Controlled Trial	60	Nov 2017 (completed)
NCT01746862[a]	A Randomized, Open-label, Two-arm Parallel Group, No Treatment Group-Controlled, Multicenter Phase III Study to Evaluate the Safety and Efficacy of Saizen® 0.067 mg/kg/Day subcutaneous Injection in Children with Idiopathic Short Stature	90	Mar 2015 (completed)
NCT01248416[a]	A Randomized Controlled Trial Of The Use Of Aromatase Inhibitors, Alone And In Combination With Growth Hormone In Adolescent Boys With Idiopathic Short Stature	76	Sep 2016 (completed)
NCT01897766[a]	Special Investigation for Genotropin (SGA Long-term Follow-up)	488	Feb 2017 (completed)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
J2940	Injection, somatrem, 1 mg
J2941	Injection, somatropin, 1 mg
Q0515	Injection, sermorelin acetate, 1 mcg
S9558	Home injectable therapy; growth hormone, including administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10 Diagnoses

B20	Human immunodeficiency virus [HIV] disease
E22.0	Acromegaly and pituitary gigantism
E22.1	Hyperprolactinemia
E22.2	Syndrome of inappropriate secretion of antidiuretic hormone
E23.0	Hypopituitarism
E23.1	Drug-induced hypopituitarism
E23.6	Other disorders of pituitary gland
E24.1	Nelson's syndrome
E89.3	Postprocedural hypopituitarism
K91.2	Postsurgical malabsorption, not elsewhere classified
N18.3	Chronic kidney disease, stage 3 (moderate)
N18.4	Chronic kidney disease, stage 4 (severe)
N18.5	Chronic kidney disease, stage 5
N18.6	End stage renal disease
P70.4	Other neonatal hypoglycemia
R62.52	Short stature (child)
Q87.1	Congenital malformation syndromes predominately associated with short stature
Q96.9	Turner's syndrome, unspecified
T20.311A	Burn of third degree of right ear [any part, except ear drum], initial encounter
T20.311D	Burn of third degree of right ear [any part, except ear drum], subsequent encounter
T20.311S	Burn of third degree of right ear [any part, except ear drum], sequela
T20.312A	Burn of third degree of left ear [any part, except ear drum], initial encounter
T20.312D	Burn of third degree of left ear [any part, except ear drum], subsequent encounter
T20.312S	Burn of third degree of left ear [any part, except ear drum], sequela
T20.32XA	Burn of third degree of lip(s), initial encounter
T20.32XD	Burn of third degree of lip(s), subsequent encounter
T20.32XS	Burn of third degree of lip(s), sequela
T20.33XA	Burn of third degree of chin, initial encounter
T20.33XD	Burn of third degree of chin, subsequent encounter
T20.33XS	Burn of third degree of chin, sequela

T20.34XA Burn of third degree of nose (septum), initial encounter
T20.34XD Burn of third degree of nose (septum), subsequent encounter
T20.34XS Burn of third degree of nose (septum), sequela
T20.35XA Burn of third degree of scalp [any part], initial encounter
T20.35XD Burn of third degree of scalp [any part], subsequent encounter
T20.35XS Burn of third degree of scalp [any part], sequela
T20.36XA Burn of third degree of forehead and cheek, initial encounter
T20.36XD Burn of third degree of forehead and cheek, subsequent encounter
T20.36XS Burn of third degree of forehead and cheek, sequela
T20.37XA Burn of third degree of neck, initial encounter
T20.37XD Burn of third degree of neck, subsequent encounter
T20.37XS Burn of third degree of neck, sequela
T20.39XA Burn of third degree of multiple sites of head, face, and neck, initial encounter
T20.39XD Burn of third degree of multiple sites of head, face, and neck, subsequent encounter
T20.39XS Burn of third degree of multiple sites of head, face, and neck, sequela
T22.311A Burn of third degree of right forearm, initial encounter
T22.311D Burn of third degree of right forearm, subsequent encounter
T22.311S Burn of third degree of right forearm, sequela
T22.312A Burn of third degree of left forearm, initial encounter
T22.312D Burn of third degree of left forearm, subsequent encounter
T22.312S Burn of third degree of left forearm, sequela
T22.321A Burn of third degree of right elbow, initial encounter
T22.321D Burn of third degree of right elbow, subsequent encounter
T22.321S Burn of third degree of right elbow, sequela
T22.322A Burn of third degree of left elbow, initial encounter
T22.322D Burn of third degree of left elbow, subsequent encounter
T22.322S Burn of third degree of left elbow, sequela
T22.331A Burn of third degree of right upper arm, initial encounter
T22.331D Burn of third degree of right upper arm, subsequent encounter
T22.331S Burn of third degree of right upper arm, sequela
T22.332A Burn of third degree of left upper arm, initial encounter
T22.332D Burn of third degree of left upper arm, subsequent encounter
T22.332S Burn of third degree of left upper arm, sequela
T22.341A Burn of third degree of right axilla, initial encounter
T22.341D Burn of third degree of right axilla, subsequent encounter
T22.341S Burn of third degree of right axilla, sequela
T22.342A Burn of third degree of left axilla, initial encounter
T22.342D Burn of third degree of left axilla, subsequent encounter
T22.342S Burn of third degree of left axilla, sequela
T22.351A Burn of third degree of right shoulder, initial encounter
T22.351D Burn of third degree of right shoulder, subsequent encounter
T22.351S Burn of third degree of right shoulder, sequela
T22.352A Burn of third degree of left shoulder, initial encounter
T22.352D Burn of third degree of left shoulder, subsequent encounter
T22.352S Burn of third degree of left shoulder, sequela
T22.361A Burn of third degree of right scapular region, initial encounter
T22.361D Burn of third degree of right scapular region, subsequent encounter
T22.361S Burn of third degree of right scapular region, sequela
T22.362A Burn of third degree of left scapular region, initial encounter

T22.362D Burn of third degree of left scapular region, subsequent encounter
T22.362S Burn of third degree of left scapular region, sequela
T22.391A Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, initial encounter
T22.391D Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, subsequent encounter
T22.391S Burn of third degree of multiple sites of right shoulder and upper limb, except wrist and hand, sequela
T22.392A Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, initial encounter
T22.392D Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, subsequent encounter
T22.392S Burn of third degree of multiple sites of left shoulder and upper limb, except wrist and hand, sequela
T23.311A Burn of third degree of right thumb (nail), initial encounter
T23.311D Burn of third degree of right thumb (nail), subsequent encounter
T23.311S Burn of third degree of right thumb (nail), sequela
T23.312A Burn of third degree of left thumb (nail), initial encounter
T23.312D Burn of third degree of left thumb (nail), subsequent encounter
T23.312S Burn of third degree of left thumb (nail), sequela
T23.321A Burn of third degree of single right finger (nail) except thumb, initial encounter
T23.321D Burn of third degree of single right finger (nail) except thumb, subsequent encounter
T23.321S Burn of third degree of single right finger (nail) except thumb, sequela
T23.322A Burn of third degree of single left finger (nail) except thumb, initial encounter
T23.322D Burn of third degree of single left finger (nail) except thumb, subsequent encounter
T23.322S Burn of third degree of single left finger (nail) except thumb, sequela
T23.331A Burn of third degree of multiple right fingers (nail), not including thumb, initial encounter
T23.331D Burn of third degree of multiple right fingers (nail), not including thumb, subsequent encounter
T23.331S Burn of third degree of multiple right fingers (nail), not including thumb, sequela
T23.332A Burn of third degree of multiple left fingers (nail), not including thumb, initial encounter
T23.332D Burn of third degree of multiple left fingers (nail), not including thumb, subsequent encounter
T23.332S Burn of third degree of multiple left fingers (nail), not including thumb, sequela
T23.341A Burn of third degree of multiple right fingers (nail), including thumb, initial encounter
T23.341D Burn of third degree of multiple right fingers (nail), including thumb, subsequent encounter
T23.341S Burn of third degree of multiple right fingers (nail), including thumb, sequela
T23.342A Burn of third degree of multiple left fingers (nail), including thumb, initial encounter
T23.342D Burn of third degree of multiple left fingers (nail), including thumb, subsequent encounter
T23.342S Burn of third degree of multiple left fingers (nail), including thumb, sequela
T23.351A Burn of third degree of right palm, initial encounter
T23.351D Burn of third degree of right palm, subsequent encounter

T23.351S Burn of third degree of right palm, sequela
T23.352A Burn of third degree of left palm, initial encounter
T23.352D Burn of third degree of left palm, subsequent encounter
T23.352S Burn of third degree of left palm, sequela
T23.361A Burn of third degree of back of right hand, initial encounter
T23.361D Burn of third degree of back of right hand, subsequent encounter
T23.361S Burn of third degree of back of right hand, sequela
T23.362A Burn of third degree of back of left hand, initial encounter
T23.362D Burn of third degree of back of left hand, subsequent encounter
T23.362S Burn of third degree of back of left hand, sequela
T23.371A Burn of third degree of right wrist, initial encounter
T23.371D Burn of third degree of right wrist, subsequent encounter
T23.371S Burn of third degree of right wrist, sequela
T23.372A Burn of third degree of left wrist, initial encounter
T23.372D Burn of third degree of left wrist, subsequent encounter
T23.372S Burn of third degree of left wrist, sequela
T23.391A Burn of third degree of multiple sites of right wrist and hand, initial encounter
T23.391D Burn of third degree of multiple sites of right wrist and hand, subsequent encounter
T23.391S Burn of third degree of multiple sites of right wrist and hand, sequela
T23.392A Burn of third degree of multiple sites of left wrist and hand, initial encounter
T23.392D Burn of third degree of multiple sites of left wrist and hand, subsequent encounter
T23.392S Burn of third degree of multiple sites of left wrist and hand, sequel
T24.301A Burn of third degree of unspecified site of right lower limb, except ankle and foot, initial encounter
T24.301D Burn of third degree of unspecified site of right lower limb, except ankle and foot, subsequent encounter
T24.301S Burn of third degree of unspecified site of right lower limb, except ankle and foot, sequela
T24.302A Burn of third degree of unspecified site of left lower limb, except ankle and foot, initial encounter
T24.302D Burn of third degree of unspecified site of left lower limb, except ankle and foot, subsequent encounter
T24.302S Burn of third degree of unspecified site of left lower limb, except ankle and foot, sequela
T24.311A Burn of third degree of right thigh, initial encounter
T24.311D Burn of third degree of right thigh, subsequent encounter
T24.311S Burn of third degree of right thigh, sequela
T24.312A Burn of third degree of left thigh, initial encounter
T24.312D Burn of third degree of left thigh, subsequent encounter
T24.312S Burn of third degree of left thigh, sequela
T24.321A Burn of third degree of right knee, initial encounter
T24.321D Burn of third degree of right knee, subsequent encounter
T24.321S Burn of third degree of right knee, sequela
T24.322A Burn of third degree of left knee, initial encounter
T24.322D Burn of third degree of left knee, subsequent encounter
T24.322S Burn of third degree of left knee, sequela
T24.331A Burn of third degree of right lower leg, initial encounter
T24.331D Burn of third degree of right lower leg, subsequent encounter
T24.331S Burn of third degree of right lower leg, sequela

T24.332A Burn of third degree of left lower leg, initial encounter
T24.332D Burn of third degree of left lower leg, subsequent encounter
T24.332S Burn of third degree of left lower leg, sequela
T24.391A Burn of third degree of multiple sites of right lower limb, except ankle and foot, initial encounter
T24.391D Burn of third degree of multiple sites of right lower limb, except ankle and foot, subsequent encounter
T24.391S Burn of third degree of multiple sites of right lower limb, except ankle and foot, sequela
T24.392A Burn of third degree of multiple sites of left lower limb, except ankle and foot, initial encounter
T24.392D Burn of third degree of multiple sites of left lower limb, except ankle and foot, subsequent encounter
T24.392S Burn of third degree of multiple sites of left lower limb, except ankle and foot, sequela
T25.311A Burn of third degree of right ankle, initial encounter
T25.311D Burn of third degree of right ankle, subsequent encounter
T25.311S Burn of third degree of right ankle, sequela
T25.312A Burn of third degree of left ankle, initial encounter
T25.312D Burn of third degree of left ankle, subsequent encounter
T25.312S Burn of third degree of left ankle, sequela
T25.321A Burn of third degree of right foot, initial encounter
T25.321D Burn of third degree of right foot, subsequent encounter
T25.321S Burn of third degree of right foot, sequela
T25.322A Burn of third degree of left foot, initial encounter
T25.322D Burn of third degree of left foot, subsequent encounter
T25.322S Burn of third degree of left foot, sequela
T25.331A Burn of third degree of right toe(s) (nail), initial encounter
T25.331D Burn of third degree of right toe(s) (nail), subsequent encounter
T25.331S Burn of third degree of right toe(s) (nail), sequela
T25.332A Burn of third degree of left toe(s) (nail), initial encounter
T25.332D Burn of third degree of left toe(s) (nail), subsequent encounter
T25.332S Burn of third degree of left toe(s) (nail), sequela
T25.391A Burn of third degree of multiple sites of right ankle and foot, initial encounter
T25.391D Burn of third degree of multiple sites of right ankle and foot, subsequent encounter
T25.391S Burn of third degree of multiple sites of right ankle and foot, sequela
T25.392A Burn of third degree of multiple sites of left ankle and foot, initial encounter
T25.392D Burn of third degree of multiple sites of left ankle and foot, subsequent encounter
T25.392S Burn of third degree of multiple sites of left ankle and foot, sequela

REVISIONS

01-30-2014	Both Pediatric and Adult Growth Hormone medical policies have been incorporated into the newly titled "Human Growth Hormone" medical policy.
	Updated Description section.
	In Policy section: • Pediatric Growth Hormone policy language was revised from the following: Growth hormone is contractually excluded except for the following specific situations: 1. Deficiency

	Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Failure to respond (GH less than 10 ng/ml) to two hormones secretagogues (arginine, clonidine, glucagon, insulin, or levodopa) b. Growth failure as defined by the following age groups: □0 - 6 months: <34 cm/year • 6 - 12 months: <15 cm/year • 1 - 3 years: <12 cm/year • Over three years to puberty (see definition of puberty below): <5 cm/year • Puberty (defined as bone age of 10 1/2 - 12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year Note: Growth rates should be tracked over at least one year. Note: Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year. 2. Insufficiency or Partial Deficiencies Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Failure to respond (GH less than 15 ng/ml) to two hormones secretagogues (arginine, clonidine, glucagon, insulin, or levodopa) b. Height less than the 2.5 percentile c. Growth failure as defined by the following age groups: • 0 – 6 months: <34 cm/year • 6 – 12 months: <15 cm/year • 1 - 3 years: <12 cm/year • Over three years to puberty (see definition of puberty below): < 5 cm/year • Puberty (defined as bone age of 10 1/2 -12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year Note: Growth rates should be tracked over at least one year. Note: Continuation of treatment with growth hormone therapy requires a growth rate above 2.5 cm/year. 3. Panhypopituitarism Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Deficiencies of 2 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) b. Low values for IGF-1 Note: Growth hormone stimulation testing is not required in these cases. Note: Growth hormone therapy may be approved for life. 4. Turner, Prader-Willi, and Noonan Syndromes With Growth Failure Growth hormone has been approved for reimbursement subject to meeting all of the following criteria: a. Height less than the 2.5 percentile for age and sex b. Growth failure as defined by the following age groups: • 0 – 6 months: < 34 cm/year • 6 – 12 months: < 15 cm/year • 1 - 3 years: <12 cm/year • Over three years to puberty (see below definition of puberty): <5 cm/year • Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year Note: Growth rates should be tracked over at least one year. Note: Growth hormone stimulation testing is not required in these cases. 5. Managing Ongoing Renal Dialysis Patients With Growth Failure Growth hormone has been approved for reimbursement subject to meeting all of the following criteria:

	a. End stage renal disease with GFR less than 75 ml/min/1.73m2 prior to successful transplant b. Under age 18 c. With open epiphyses d. Height less than the 2.5 percentile for age and sex e. Growth failure as defined by the following age groups: • 0 – 6 months: <34 cm/year • 6 – 12 months: < 15 cm/year ☐1 – 3 years: <12 cm/year • Over three years to puberty (see below definition of puberty): <5 cm/year • Puberty (defined as bone age of 10 1/2-12 years for girls and bone age of 12 1/2 -14 1/2 years for boys): <6 cm/year f. Complicating factors have been treated including malnutrition and acidosis Note: Growth rates should be tracked over at least one year. Note: Growth Hormone stimulation testing is not required. <u>Termination of Growth Hormone Therapy</u> Growth hormone therapy is no longer covered when any one of the following criteria is met: 1. Epiphyseal fusion has occurred 2. Mid-parental height is achieved. Mid-parental height = (father's height + mother's height) divided by 2, plus 2.5 inches (6.4 cm) (male) or minus 2.5 inches (6.4 cm) (female) 3. Failure to respond to growth hormone therapy with a growth rate of less than 2.5 cm/year NOTE: When a consultant recommends that growth hormone treatment be given for the life of the patient, it will no longer be necessary to re-review for medical necessity. It will be necessary, however, to review for benefits. Such instances may include: 1. Panhypopituitarism, or 2. When adult growth hormone therapy requirements are met (see Adult Growth Hormone policy) Documentation needed for predetermination are: <u>DOCUMENTATION</u> • Growth charts with at least 3 measurements over at least one year • Growth hormone stimulation testing results • Adult Growth Hormone policy language was revised from the following: 1. Growth hormone therapy is excluded for insureds over the age of 18 with the following exceptions: a. Those Insureds over the age 18 with: • Demonstrated hypothalamic or pituitary disease or injury; and • Laboratory proven growth hormone deficiency b. Those Insureds over the age of 18 who have had childhood onset of growth hormone deficiency and have had that deficiency demonstrated by testing during childhood. c. Those Insureds over the age 18 with Panhypopituitarism with deficiencies of 3 or more other pituitary hormones (TSH, ACTH, FSH/LH, antidiuretic hormone) and low values for IGF-1. 2. Growth hormone deficiency must be documented by the following criteria: a. Biochemical testing by means of a subnormal response to standard growth hormone stimulation test (peak growth hormone values <5ng/ml to provocative stimuli). Insulin tolerance test with documented hypoglycemia (blood sugars less that 40mg/dl or 50% decrease from baseline) with symptoms is the standard test. When Insulin Tolerance test is contraindicated in a given insured, Growth Hormone Releasing Hormone/arginine can be used as an alternate testing procedure. L-dopa, glucagon or clonidine is not acceptable secretagogues in adults.

	OR b. A below normal level of IGF-1 (less than 84 µg/liter) constitutes laboratory proof of growth hormone deficiency when associated with panhypopituitarism with documented multiple hormone deficiencies (3 or more deficiencies: secondary hypothyroidism, ACTH deficiency, gonadotropin deficiency, diabetes insipidus) as a result of pituitary or hypothalamic disease secondary to tumor, surgery, inflammation, radiation therapy, severe head trauma or structural abnormality (septo-optic dysplasia, ectopic neurohypophysis). Growth hormone stimulation testing is not necessary in these cases. 3. Continuation of approval for growth hormone therapy requires some indication of a clinical response to the growth hormone during the first 12 months of therapy; weight loss, improvement on lipid profile, increased bone mass, increased muscle strength or increase of IGF1 into the normal range. Children on growth hormone therapy who continue growth hormone therapy into adulthood or adults with hypopituitarism of recent onset will not exhibit the sequelae of adult growth hormone deficiency and will not show the improvements listed above. NOTE: If consultant decides that growth hormone treatment will be given for the rest of the life of the patient, it will no longer be necessary for Medical Review to re-review for medical necessity. It will be necessary, however, to review for benefits. <u>UTILIZATION</u> If growth hormone is approved for an adult, and there has been demonstrative clinical improvement maintained for 1 year or more, periodic review beyond that will be unnecessary for these adults.
	Updated Rationale section.
	In Coding section: ▪ Removed CPT code 90772 (Deleted code 01-01-2009). ▪ Added ICD-10 diagnosis codes. *(Effective October 1, 2014)*
	Updated References section.
12-09-2014	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Under ICD-10 diagnoses, changed effective date to "October 1, 2015".
	Updated References section.
06-23-2015	Updated Description section.
12-08-2015	Updated Description section.
	Updated Rationale section.
	Updated References section.
01-01-2017	Updated Description section.
	In Policy section: ▪ Added Item A 5, "Neonate (≤4 months of age) with hypoglycemia in the absence of metabolic disorder AND growth hormone level is <20 ng/mL. ▪ Added Item A 6, "AIDS wasting." ▪ Added Item A 7, "Prevention of growth delay in children with severe burns (see Policy Guidelines). ▪ Added Item A 8, "Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines). ▪ Added Item B 4, "AIDS wasting." ▪ Added Item B 5, "Promotion of wound healing in patients with severe burns (see Policy Guidelines)."

	▪ Added Item B 6, "Short bowel syndrome receiving specialized nutritional support in conjunction with optimal management of short bowel syndrome (see Policy Guidelines.)" ▪ In Policy Guidelines Item 3, added "Sleep studies are recommended prior to initiation of growth hormone therapy for obese pediatric patients with Prader-Willi syndrome." ▪ Added Policy Guidelines Items 5, 6, and 7. ▪ Added Policy Guidelines Item 8 e, "Neonatal hypoglycemia related to growth hormone deficiency." ▪ In Policy Guidelines Item 8, added "Children, Adolescents and Adults: a. AIDS wasting syndrome b. Short Bowel syndrome c. Severe burn patients"
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 codes: B20, K91.2, P70.4, R62.52, T20.311A-S, T20.312A-S, T20.32XA-S, T20.33XA-S, T20.34XA-S, T20.35XA-S, T20.36XA-S, T20.37XA-S, T20.39XA-S, T22.311A-S, T22.312A-S, T22.321A-S, T22.322A-S, T22.331A-S, T22.332A-S, T22.341A-S, T22.342A-S, T22.351A-S, T22.352A-S, T22.361A-S, T22.362A-S, T22.391A-S, T22.392A-S, T23.311A-S, T23.312A-S, T23.321A-S, T23.322A-S, T23.331A-S, T23.332A-S, T23.341A-S, T23.342A-S, T23.351A-S, T23.352A-S, T23.361A-S, T23.362A-S, T23.371A-S, T23.372A-S, T23.391A-S, T23.392A-S, T24.301A-S, T24.302A-S, T24.311A-S, T24.312A-S, T24.321A-S, T24.322A-S, T24.331A-S, T24.332A-S, T24.391A-S, T24.392A-S, T25.311A-S, T25.312A-S, T25.321A-S, T25.322A-S, T25.331A-S, T25.332A-S, T25.391A-S, T25.392A-S.
	Updated References section.
05-24-2017	Updated Description section.
08-18-2017	In Policy section: ▪ In Item A 1, added "as defined by" and removed "meeting the following criteria" to read, "Growth Hormone or Insufficiency as defined by:" ▪ In Item A 4, added "Chronic Renal Insufficiency or End Stage Renal Disease" and "as defined by" and removed "Managing Ongoing Renal Dialysis Patients With Growth Failure" and "subject to meeting all of the following criteria" to read, "Chronic Renal Insufficiency or End Stage Renal Disease as defined by:" ▪ Added new Item A 4 a, "Chronic renal insufficiency defined as GFR less than 60 mL/min/1.73 m^2 prior to successful transplant" ▪ In new Item A 4 b (previous Item A 4 a), added "defined as" and removed "with" to read, "End stage renal disease defined as serum creatinine greater than 1.5 mg/dL or GFR less than 75 mL/min/1.73 m^2 prior to successful transplant" ▪ Removed previous Item A 4 b, "Under age 18" ▪ In Item A Termination of Growth Hormone Therapy, removed "no longer covered" and added "not medically necessary" to read, "Growth hormone therapy is not medically necessary when any of the following criteria is met"
12-20-2017	Updated Description section.
	In Policy section: ▪ Added "A Nonpreferred Growth Hormone will be approved when BOTH of the following are met: 1. The patient's medication history indicates use of the *preferred* growth hormone (GH) agent and 2. The patient has documented intolerance, FDA labeled contraindication, or hypersensitivity to the *preferred* GH agent."
	Updated Rationale section.
	In Coding section: ▪ Added coding bullets. ▪ ICD-9 codes removed.
	Updated References section.
12-05-2018	Updated Description section.
	Updated Rationale section.
	In Coding section:

	▪ Removed coding bullets.
	Updated References section.

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